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 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  FEB 27   New STN AnaVist pricing effective March 1, 2006
 NEWS  4  MAY 10   CA/CAplus enhanced with 1900-1906 U.S. patent records
 NEWS  5  MAY 11   KOREAPAT updates resume
 NEWS  6  MAY 19   Derwent World Patents Index to be reloaded and enhanced
 NEWS  7  MAY 30   IPC 8 Rolled-up Core codes added to CA/CAplus and
                   USPATFULL/USPAT2
 NEWS  8  MAY 30   The F-Term thesaurus is now available in CA/CAplus
 NEWS  9  JUN 02   The first reclassification of IPC codes now complete in
                   INPADOC
 NEWS 10  JUN 26   TULSA/TULSA2 reloaded and enhanced with new search and
                   and display fields
 NEWS 11  JUN 28   Price changes in full-text patent databases EPFULL and PCTFULL
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 NEWS 13  JUl 14   FSTA enhanced with Japanese patents
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 NEWS 18  SEP 11   CA/CAplus enhanced with more pre-1907 records
 NEWS 19  SEP 21   CA/CAplus fields enhanced with simultaneous left and right
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 NEWS 20  SEP 25   CA(SM)/CAplus(SM) display of CA Lexicon enhanced
 NEWS 21  SEP 25   CAS REGISTRY(SM) no longer includes Concord 3D coordinates
 NEWS 22  SEP 25   CAS REGISTRY(SM) updated with amino acid codes for pyrrolysine

 NEWS EXPRESS  JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

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FILE 'HOME' ENTERED AT 20:15:09 ON 27 SEP 2006

=> file uspatful
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 26 Sep 2006 (20060926/PD)
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=> e huston james s/in
E1            1     HUSTON JAMES J/IN
E2            6     HUSTON JAMES R/IN
E3           26 --> HUSTON JAMES S/IN
E4            1     HUSTON JANET/IN
E5           29     HUSTON JANET M/IN
E6            1     HUSTON JARED M/IN
E7            1     HUSTON JERRY D/IN
E8            5     HUSTON JOEL/IN
E9            9     HUSTON JOEL M/IN
E10           1     HUSTON JOHN L/IN
E11          10     HUSTON JOHN T/IN
E12           1     HUSTON JOHN TIMOTHY/IN

=> s e3
L1           26 "HUSTON JAMES S"/IN

=> s l1 and (framework region?/clm)
         15274 FRAMEWORK/CLM
        367861 REGION?/CLM
           380 FRAMEWORK REGION?/CLM
                 ((FRAMEWORK(W)REGION?)/CLM)
L2             7 L1 AND (FRAMEWORK REGION?/CLM)

=> d l2,cbib,clm,1-7

L2   ANSWER 1 OF 7  USPATFULL on STN
2006:173999 Biosynthetic binding proteins for immuno-targeting.
    Huston, James S., Chestnut Hill, MA, UNITED STATES
    Houston, Lou L., Oakland, CA, UNITED STATES
    Ring, David B., Redwood City, CA, UNITED STATES
    Oppermann, Hermann, Medway, MA, UNITED STATES
    US 2006147444 A1 20060706
    APPLICATION: US 2003-684237  A1  20031010 (10)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A formulation for targeting an epitope on an antigen expressed in a
       mammal, the formulation comprising a pharmaceutically acceptable carrier
       in combination with,  a dimeric biosynthetic construct for binding at
       least one preselected antigen, the construct comprising:  (a) two
       polypeptide chains, each of which have:  an amino acid sequence defining
       at least two polypeptide domains, connected by a polypeptide linker
       spanning the distance between the C-terminus of one domain and the
       N-terminus of the other, the amino acid sequence of each said domain
       comprising complementarity determining regions (CDRs) interposed between
       framework regions (FRs), the CDRs and FRs of each polypeptide chain
       together defining a binding site immunologically reactive with a said
       preselected antigen, and  and a C-terminal tail having a
       non-self-associating structure under physiological conditions and
       comprising at least a crosslinking means, and  (b) a linkage coupling
       said crosslinking means on said two polypeptide chains,  said dimeric
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construct having a conformation permitting binding of a said preselected antigen by the binding site of each said polypeptide chain when administered to said mammal.

2. A formulation for targeting an epitope on an antigen expressed in a mammal, the formulation comprising a pharmaceutically acceptable carrier in combination with, a dimeric biosynthetic construct for binding preferentially to a preselected antigen, the construct comprising: (a) two polypeptide chains, each of which have: an amino acid sequence defining at least two polypeptide domains, connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions**.(FRs), the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with a said preselected antigen, and a C-terminal tail having a non-self-associating structure under physiological conditions and comprising at least a crosslinking means, and (b) a linkage coupling said crosslinking means to form a homodimeric construct, said homodimeric construct having a conformation permitting binding to said preselected antigen in said mammal with an avidity greater than the avidity of either of said polypeptide chains individually.

3. A polypeptide chain for binding preferentially to a preselected antigen, the polypeptide chain comprising: an amino acid sequence defining at least two polypeptide domains, connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRS) interposed between **framework regions** (FRs), the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with said preselected antigen, and a C-terminal tail having a non-self-associating structure under physiological conditions and comprising at least a crosslinking means.

4. The polypeptide chain of claim 1, 2 or 3 wherein said C-terminal tail comprises the amino acid sequence Ser-Cys.

5. The polypeptide chain of claim 1, 2 or 3 wherein said C-terminal tail comprises the amino acid sequence $(Gly)_4$-Cys.

6. The polypeptide chain of claim 1, 2 or 3 wherein said C-terminal tail comprises the amino acid sequence $(His)_6$-$(Gly)_4$-Cys.

7. The polypeptide chain of claim 1, 2 or 3 wherein said C-terminal tail can chelate one or more ions.

8. The polypeptide chain of claim 7 wherein said ion is a metal ion.

9. The polypeptide chain of claim 1, 2 or 3 wherein said crosslinking means is a derivatizable amino acid side chain.

10. The polypeptide chain of claim 9 wherein said derivatizable amino acid is selected from the group consisting of lysine, arginine and histidine.

11. The polypeptide chain of claim 9 wherein said derivatizable amino acid is a cysteine amino acid.

12. The polypeptide chain of claim 1, 2 or 3 wherein said crosslinking means comprises a posttranslationally modified amino acid.

13. The polypeptide chain of claim 12 wherein said posttranslationally modified amino acid is the Asn residue located in the amino acid sequence selected form group of Asn-Xaa-Ser and Asn-Xaa-Thr.

14. The formulation of claim 1 or 2 wherein said linkage is a chemical bridge.

15. The formulation of claim 1 or 2 wherein said linkage comprises a disulfide bond.

16. The formulation of claim 1 or 2 wherein said linkage comprises a bismaleimidohexane cross-linker.

17. The formulation of claim 1 or 2 wherein said linkage comprises a bismaleimidocaproyl amino acid linker.

18. The formulation of claim 1 or 2 wherein said linkage comprises a peptidyl linker.

19. The formulation of claim 1 or 2 wherein said linkage forms a substantially inflexible structure under physiological conditions.

20. The formulation of claim 1 or 2 wherein said linkage has a length and composition optimized for binding of two preselected antigens expressed on a tissue surface in a mammal.

21. The formulation of claim 1 or 2 wherein said linkage comprises a detectable moiety.

22. The formulation of claim 21 wherein said detectable moiety comprises Technetium-99m.

23. The formulation of claim 21 wherein said detectable moiety comprises means for inducing proton relaxation in vivo.

24. The formulation of claim 1 or 2 wherein said dimeric biosynthetic construct targets said epitope on said antigen with an avidity greater than that of a monoclonal antibody having the same antigenic determinant as said construct, or a fragment thereof.

25. The formulation of claim 1 or 2 wherein said dimeric biosynthetic construct targets said epitope on said antigen with an avidity greater than that of either of said polypeptide chains individually.

26. The formulation of claim 1 or 2 wherein said preselected antigen is expressed on the surface of a cell.

27. The formulation of claim 1 or 2 wherein said antigen is an intracellular component exposed upon cell lysis.

28. The formulation of claim 1 or 2 wherein said dimeric construct binds two different epitopes.

29. The formulation of claim 1 or 2 wherein one of said binding sites further comprises a catalytic site.

30. The formulation of claim 1 or 2 wherein one of said binding sites binds an epitope on a therapeutic agent to be targeted to a cell surface.

31. The formulation of claim 30 wherein said therapeutic agent is a cytotoxic agent.

32. The formulation of claim 1, 2 or 3 wherein said construct has improved in vivo imaging characteristics.

33-49. (canceled)

L2 ANSWER 2 OF 7 USPATFULL on STN
2005:68500 Biosynthetic binding proteins for immuno-targeting.
Huston, James S., Newton Lower Falls, MA, UNITED STATES
Oppermann, Hermann, Medway, MA, UNITED STATES
US 2005058638 A1 20050317
APPLICATION: US 2003-683547 A1 20031010 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An isolated polypeptide including an antigen binding site, the polypeptide comprising: (a) two variable domain sequences, each variable domain sequence independently comprising at least one group of three complementarity determining regions (CDRs) interposed between **framework regions** (FRs), which variable domains are linked to a polypeptide linker to form a single polypeptide chain in which said framework and complementarity determining regions together define a variable region binding domain which can be immunologically reactive with an antigen, and (b) an amino acid sequence that is a part of said single polypeptide chain, and has a biological activity independent of said immunological reactivity.

2. The polypeptide of claim 1, wherein said **framework regions** are from human immunoglobulin sequences.

3. The polypeptide of claim 1, wherein at least some of said complementarity determining regions are from human immunoglobulin sequences.

4. The polypeptide of claim 1, wherein said variable domain sequences are from human immunoglobulin sequences.

5. The polypeptide of claim 1, wherein at least some of said variable domain sequences are from human immunoglobulin sequences.

L2 ANSWER 3 OF 7 USPATFULL on STN
2002:300832 Biosynthetic binding proteins for immuno-targeting.
Huston, James S., Chestnut Hill, MA, UNITED STATES
Houston, L. L., Oakland, CA, UNITED STATES
Ring, David B., Redwood City, CA, UNITED STATES
Oppermann, Hermann, Medway, MA, UNITED STATES
Chiron Corporation (U.S. corporation)
US 2002168375 A1 20021114
APPLICATION: US 2001-887853 A1 20010621 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A formulation for targeting an epitope on an antigen expressed in a mammal, the formulation comprising a pharmaceutically acceptable carrier in combination with, a dimeric biosynthetic construct for binding at least one preselected antigen, the construct comprising: (a) two polypeptide chains, each of which have: an amino acid sequence defining at least two polypeptide domains, connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain

comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with a said preselected antigen, and and a C-terminal tail having a non-self-associating structure under physiological conditions and comprising at least a crosslinking means, and (b) a linkage coupling said crosslinking means on said two polypeptide chains, said dimeric construct having a conformation permitting binding of a said preselected antigen by the binding site of each said polypeptide chain when administered to said mammal.

2. A formulation for targeting an epitope on an antigen expressed in a mammal, the formulation comprising a pharmaceutically acceptable carrier in combination with, a dimeric biosynthetic construct for binding preferentially to a preselected antigen, the construct comprising: (a) two polypeptide chains, each of which have: an amino acid sequence defining at least two polypeptide domains, connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with a said preselected antigen, and a C-terminal tail having a non-self-associating structure under physiological conditions and comprising at least a crosslinking means, and (b) a linkage coupling said crosslinking means to form a homodimeric construct, said homodimeric construct having a conformation permitting binding to said preselected antigen in said mammal with an avidity greater than the avidity of either of said polypeptide chains individually.

3. A polypeptide chain for binding preferentially to a preselected antigen, the polypeptide chain comprising: an amino acid sequence defining at least two polypeptide domains, connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRS) interposed between **framework regions** (FRs), the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with said preselected antigen, and a C-terminal tail having a non-self-associating structure under physiological conditions and comprising at least a crosslinking means.

4. The polypeptide chain of claim 1, 2 or 3 wherein said C-terminal tail comprises the amino acid sequence Ser-Cys.

5. The polypeptide chain of claim 1, 2 or 3 wherein said C-terminal tail comprises the amino acid sequence $(Gly)_4$-Cys.

6. The polypeptide chain of claim 1, 2 or 3 wherein said C-terminal tail comprises the amino acid sequence $(His)_6$-$(Gly)_4$-Cys.

7. The polypeptide chain of claim 1, 2 or 3 wherein said C-terminal tail can chelate one or more Ions.

8. The polypeptide chain of claim 7 wherein said ion is a metal ion.

9. The polypeptide chain of claim 1, 2 or 3 wherein said crosslinking means is a derivatizable amino acid side chain.

10. The polypeptide chain of claim 9 wherein said derivatizable amino acid is selected from the group consisting of lysine, arginine and histidine.

11. The polypeptide chain of claim 9 wherein said derivatizable amino acid is a cysteine amino acid.

12. The polypeptide chain of claim 1, 2 or 3 wherein said crosslinking means comprises a posttranslationally modified amino acid.

13. The polypeptide chain of claim 12 wherein said posttranslationally modified amino acid is the Asn residue located in the amino acid sequence selected form group of Asn--Xaa--Ser and Asn--Xaa--Thr.

14. The formulation of claim 1 or 2 wherein said linkage is a chemical bridge.

15. The formulation of claim 1 or 2 wherein said linkage comprises a disulfide bond.

16. The formulation of claim 1 or 2 wherein said linkage comprises a bismaleimidohexane cross-linker.

17. The formulation of claim 1 or 2 wherein said linkage comprises a bismaleimidocaproyl amino acid linker.

18. The formulation of claim 1 or 2 wherein said linkage comprises a peptidyl linker.

19. The formulation of claim 1 or 2 wherein said linkage forms a substantially inflexible structure under physiological conditions.,

20. The formulation of claim 1 or 2 wherein said linkage has a length and composition optimized for binding of two preselected antigens expressed on a tissue surface in a mammal.

21. The formulation of claim 1 or 2 wherein said linkage comprises a detectable moiety.

22. The formulation of claim 21 wherein said detectable moiety comprises Technetium-99m.

23. The formulation of claim 21 wherein said detectable moiety comprises means for inducing proton relaxation in vivo.

24. The formulation of claim 1 or 2 wherein said dimeric biosynthetic construct targets said epitope on said antigen with an avidity greater than that of a monoclonal antibody having the same antigenic determinant as said construct, or a fragment thereof.

25. The formulation of claim 1 or 2 wherein said dimeric biosynthetic construct targets said epitope on said antigen with an avidity greater than that of either of said polypeptide chains individually.

26. The formulation of claim 1 or 2 wherein said preselected antigen is expressed on the surface of a cell.

27. The formulation of claim 1 or 2 wherein said antigen is an intracellular component exposed upon cell lysis.

28. The formulation of claim 1 or 2 wherein said dimeric construct binds two different epitopes.

29. The formulation of claim 1 or 2 wherein one of said binding sites further comprises a catalytic site.

30. The formulation of claim 1 or 2 wherein one of said binding sites binds an epitope on a therapeutic agent to be targeted to a cell surface.

31. The formulation of claim 30 wherein said therapeutic agent is a cytotoxic agent.

32. The formulation of claim 1, 2 or 3 wherein said construct has improved in vivo imaging characteristics.

33. A single-chain Fv (sFv) polypeptide for binding preferentially to a c-erbB-2 or a c-erbB-2-related tumor antigen, the polypeptide comprising: an amino acid sequence defining at least two polypeptide domains, connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with said c-erbB-2 or c-erbB-2-related tumor antigen.

34. The polypeptide chain of claim 1, 2, 3 or 33 wherein said FR sequences are derived from a human immunoglobulin.

35. The polypeptide chain of claim 1, 2, 3 or 33 wherein said CDR sequences are derived from an immunoglobulin that binds c-erbB-2 or a c-erbB-2 related antigen.

36. The polypeptide chain of claim 35 wherein said CDR sequences are derived from an immunoglobulin selected from the group consisting of the monoclonal antibodies 520C9, 741F8, and 454C11.

37. The polypeptide chain of claim 1, 2, or 3 having the amino acid sequence found in SEQ ID NO. 1.

38. The polypeptide chain of claim 33 having the amino acid sequence defined by residues 1 through 245 in SEQ ID NO. 1.

39. The polypeptide chain of claim 1, 2, 3 or 33 further comprising a detectable moiety.

40. The polypeptide chain of claim 39 wherein said detectable moiety comprises a radioactive atom.

41. The polypeptide chain of claim 40 wherein said detectable moiety comprises TechnetCium-99m,

42. A DNA sequence encoding the polypeptide chain of claim 1, 2, 3 or 33.

43. A host cell transfected with a DNA of claim 42.

44. A method of imaging a preselected antigen in a mammal expressing said antigen, said method comprising the steps of: (a) administering to said mammal the formulation of claim 1 or 2 having affinity for said preselected antigen, at a concentration sufficient to permit extracorporeal detection of said construct bound to said preselected antigen; and (b) detecting said polypeptide chain bound to said antigen.

45. The method of claim 44 for use in magnetic resonance imaging.

46. The formulation of claim 1 or 2 for use as an in vivo imaging agent.

47. The formation of claim 1 or 2 wherein said biosynthetic construct is capable of remaining localized to target tissue in a mammal for a longer time than either of said polypeptide chains individually.

48. A formulation for targeting an epitope on an antigen expressed in a mammal, the formulation comprising a pharmaceutically acceptable carrier in combination with, a dimeric biosynthetic construct for binding at least one preselected antigen, the construct comprising: (a) two polypeptide chains, each of which have: an amino acid sequence defining at least two polypeptide domains, connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with a said preselected antigen, and an N-terminal tail comprising at least a crosslinking means, and (b) a linkage coupling said crosslinking means on said two polypeptide chains, said dimeric construct having a conformation permitting binding of a said preselected antigen by the binding site of each said polypeptide chain when administered to said mammal.

49. A formulation for targeting an epitope on an antigen expressed in a mammal, the formulation comprising a pharmaceutically acceptable carrier in combination with, a dimeric biosynthetic construct for binding at least one preselected antigen, the construct comprising: (a) two polypeptide chains, each of which have: an amino acid sequence defining at least two polypeptide domains, connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with a said preselected antigen, said polypeptide linker further comprising a crosslinking means, and (b) a linkage coupling said crosslinking means on said two polypeptide chains, said dimeric construct having a conformation permitting binding of a said preselected antigen by the binding site of each said polypeptide chain when administered to said mammal.

L2 ANSWER 4 OF 7 USPATFULL on STN
1999:40194 Method of producing single-chain Fv molecules.
Jost, Carolina R., Washington, DC, United States
Segal, David M., Rockville, MD, United States
Huston, James S., Chestnut Hill, MA, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 5888773 19990330
APPLICATION: US 1994-292124 19940817 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A single-chain Fv antibody with antigen-binding activity comprising a light chain variable region (VL, comprising SEQ ID NO: 17, and, heavy chain varible region (VH, comprising a non-naturally occurring N-linked glycosylation site wherein an asparagine amino acid residue is substituted for lysine 19 of SEQ ID NO: 15.

2. A method of increasing the rate of secretion of a single-chain Fv antibody from mamnnalian cells, wherein the single-chain Fv antibody is modified to have a non-naturally occurring glycosyla-ion site and the antibody has antigen-binding activity, comprising the steps of: (a) modifying a polynucleic acid which encodes a single-chain Fv antibody to include a non-naturally occurring N-linked glycosylation site in the first **framework region** of VH in the encoded amino acid sequence, thereby providing a single-chain Fv construct encoding a modified single-chain Fv artibody; (b) introducing the single-chain Fv construct of step (a) into a vector which expresses said construct in a mammalian ceil and transfecting said vector containing the single-chain Fv construct into a competent mammalian cell; and (c) maintaining said cell transfected with the vector of step (b) in cell culture medium under conditions sufficient for expression of the single-chair Fv construct within the cell and secretion of the expressed modified single-chain Fv antibody from the cell into the cell culture medium, whereirn the modified single-chain Fv antibody is secreted into the cell culture medium at a faster rate than the unmodified single chain Fv antibody, and the modified single-chain Fv antibody has antigen-binding activity.

3. The method of claim 2 wnerein the non-naturally occurring glycosylation site is at position 19 of the VH **framework region**.

4. The method of claim 3 wherein the N-linked glycosylation site is Asn-X-Ser/Thr.

5. The method of claim 3 wherein the mammalian cell is selected from the group consisting of: cos-7 monkey kidney fibroblast cells; K562 human erythroleukemia cells; 293 cells; myeloma cells; and Chinese hamster ovary cells.

6. A method of producing a single-chain Fv antibody with antigen-binding activity and with an increased rate of secretion from mammalian cells, comprising the steps of: (a) modifying a polynucleic acid sequence which encodes a single-chain Fv antibody to include a non-naturally occurring N-linked glycosylation site in the first **framework region** of VH in the encoded amino acid sequence, thereby providing a single-chain Fv construct encoding a modified single-chain Fv antibody; (b) introducing the single-chain Fv construct of step (a) into a vector which expresses said construct in a mammalian cell and transfecting said vector containing the single-chain Fv construct into a competent mammalian cell; and (c) maintaining said cell transfected with the vector of step (b) in cell culture medium under conditions sufficient for expression of the single-chain Fv construct within the cell and secretion of the expressed modified single-chain Fv antibody from the cell into the cell culture medium, thereby producing a single-chain Fv antibody with antigen-binding activity and an increased rate of secretion from mammalian cells when compared with the rate of secretion of the unmodified single-chain Fv antibody.

7. A host cell transfected with a vector containing the single-chain Fv construct of claim 6.

8. A method of increasing the rate of secretion of a single-chain Fv antibody from mammalian cells comprising modifying the single-chain Fv antibody by introducing into the single-chain Fv antibody a non-naturally occurring N-linked glycosylation site in the first **framework region** of VH, and secreting the modified single-chain Fv antibody from a mammalian cell, wherein the rate of secretion of the modified single-chain Fv antibody is increased as compared to the rate of secretion of the unmodified single-chain Fv antibody, and the

modified single-chain Fv antibody retains its antigen-binding activity.

9. The method of claim 8 wherein the glycosylation site is an N-linked glycosylation site at position 19 of VH.

10. The method of claim 9 wherein the glycosylation site is Asn-x-Ser/Thr.

11. A method of producing, in mammalian cells, a single-chain Fv antibody with antigen-binding activity comprising a VL comprising SEQ ID NO: 17 and a VH comprising a non-naturally occurring N-linked gycosylation site, comprising the steps of: (a) modifying a polynucleic acid which encodes the single-chain Fv antibody comprising SEQ ID NO: 17 to include a non-naturally occurring N-linked glycosylation site in the VH, wherein the glycosylation site comprises an asparagine amino acid residue substituted for lysine 19 of SEQ ID NO: 15, thereby providing a single-chain Fv construct; (b) introducing the single-chain Fv construct of step (a) into a vector which expresses said construct in a mammalian cell and transfecting said vector containing the single-chain Fv construct into a competent mammalian cell; and (c) maintaining said cell transfected with the vector of step (b) in cell culture medium under conditions sufficient for expression of the single-chain Fv construct within the cell and secretion of the expressed single-chain Fv antibody from the cell into cell culture medium, thereby producing a single-chain Fv antibody with antigen-binding activity and a non-naturally occurring glycosylation site in the VH.

12. The method of claim 11 wherein the polynucleic acid encoding the single-chain Fv antibody comprises SEQ ID NO: 16 and SEQ ID NO: 14, wherein a codon for asparagine is substituted for the codon for lysine at position 19 of SEQ ID NO: 14.

13. A host cell transfected with a vector containing the single-chain Fv construct of claim 11.

14. A single-chain Fv antibody produced by the method of claim 11.

L2 ANSWER 5 OF 7 USPATFULL on STN
1998:144242 Biosynthetic binding proteins for immuno-targeting.
Huston, James S., Chestnut Hill, MA, United States
Houston, L. L., Oakland, CA, United States
Ring, David B., Redwood City, CA, United States
Oppermann, Hermann, Medway, MA, United States
Creative BioMolecules, Inc., Hopkinton, MA, United States (U.S. corporation)Chiron Corporation, Emeryville, CA, United States (U.S. corporation)
US 5837846 19981117
APPLICATION: US 1995-461386 19950605 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An isolated nucleic acid sequence encoding a polypeptide chain that binds preferentially to a preselected antigen, the polypeptide chain comprising: an amino acid sequence defining, (a) an sFv comprising two polypeptide domains connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of said sFv together defining a binding site that binds preferentially to said preselected

antigen, and (b) a C-terminal tail peptide bonded to the C-terminus of the sFv and having an amino acid sequence selected from the group consisting of Ser-Cys, $(Gly)_4$ -Cys, and $(His)_6$ -$(Gly)_4$ -Cys.

2. The isolated nucleic acid of claim 1, wherein the C-terminal tail comprises the amino acid sequence Ser-Cys.

3. The isolated nucleic acid of claim 1, wherein the C-terminal tail comprises the amino acid sequence $(Gly)_4$ -Cys.

4. The isolated nucleic acid of claim 1, wherein the C-terminal tail comprises the amino acid sequence $(His)_6$ -$(Gly)_4$ -Cys.

5. The isolated nucleic acid of claim 1, wherein the CDR sequences are derived from an immunoglobulin that binds c-erbB-2 or a c-erbB-2-related antigen.

6. The isolated nucleic acid of claim 5, wherein the CDR sequences are derived from an immunoglobulin selected from the group consisting of the monoclonal antibodies 520C9, 741F8, and 454C11.

7. The isolated nucleic acid of claim 1 defined by the DNA sequence set forth in Sequence ID No. 1.

8. A host cell transfected with the isolated nucleic acid of claim 1.

9. A host cell transfected with the isolated nucleic acid of claim 5.

10. A host cell transfected with the isolated nucleic acid of claim 2.

11. A host cell transfected with the isolated nucleic acid of claim 3.

12. A host cell transfected with the isolated nucleic acid of claim 4.

L2 ANSWER 6 OF 7 USPATFULL on STN
1998:54459 Biosynthetic binding proteins for immunotargeting.
Huston, James S., Chestnut Hill, MA, United States
Houston, L. L., Oakland, CA, United States
Ring, David B., Redwood City, CA, United States
Oppermann, Hermann, Medway, MA, United States
Chiron Corporation, Emeryville, CA, United States (U.S. corporation) Creative BioMolecules, Inc., Hopkinton, MA, United States (U.S. corporation)
US 5753204 19980519
APPLICATION: US 1995-461838 19950605 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of imaging a preselected antigen expressed in a mammal, said method comprising the steps of: (a) administering to said mammal at a concentration sufficient for extracorporeal detection of a said preselected antigen, a composition comprising a pharmaceutically acceptable carrier in combination with a dimeric biosynthetic construct that binds at least one preselected antigen, wherein the construct comprises two separate polypeptide chains, each of which have an amino acid sequence defining an sFv comprising two polypeptide domains connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs

and FRs of each said sFv together defining a binding site immunologically reactive with a said preselected antigen, and a C-terminal tail essentially free of helical character under physiological conditions and comprising at least one amino acid having a derivatizable amino acid side chain, and an sFv coupler linking together each said sFv through the derivatizable amino acid side chain disposed within the C-terminal tail of each said sFv, said dimeric biosynthetic construct having a conformation wherein the binding site of each said sFv is operative to bind a said preselected antigen when said dimeric biosynthetic construct is administered to said mammal; and (b) detecting said dimeric biosynthetic construct bound to a said preselected antigen.

2. The method of claim 1, wherein said dimeric biosynthetic construct further comprises a detectable moiety.

3. The method of claim 2, wherein said detectable moiety comprises a radioactive atom.

4. The method of claim 3, wherein said detectable moiety comprises Technetium-99m.

5. The method of claim 1 for use in magnetic resonance imaging.

6. The method of claim 1, wherein said preselected antigen is c-erbB-2 or a c-erbB-2 related antigen.

7. A method of imaging a preselected antigen expressed in a mammal, said method comprising the steps of: (a) administering to said mammal at a concentration sufficient for extracorporeal detection of a said preselected antigen a composition comprising a pharmaceutically acceptable carrier in combination with a dimeric biosynthetic construct that binds at least one preselected antigen wherein the construct comprises two separate polypeptide chains, each of which have an amino acid sequence defining an sFv comprising two polypeptide domains connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each said sFv together defining a binding site immunologically reactive with a said preselected antigen, and an N-terminal tail comprising at least one amino acid having a derivatizable amino acid side chain, and an sFv coupler linking together each said sFv through the derivatizable amino acid side chain disposed within the N-terminal tail of each said sFv, said dimeric biosynthetic construct having a conformation wherein the binding site of each said sFv is operative to bind a said preselected antigen when said dimeric biosynthetic construct is administered to said mammal; and (b) detecting said dimeric biosynthetic construct bound to a said preselected antigen.

8. The method of claim 7, wherein said dimeric biosynthetic construct further comprises a detectable moiety.

9. The method of claim 8, wherein said detectable moiety comprises a radioactive atom.

10. The method of claim 9, wherein said detectable moiety comprises Technetium-99m.

11. The method of claim 7, for use in magnetic resonance imaging.

12. The method of claim 7, wherein said preselected antigen is c-erbB-2 or a c-erbB-2 related antigen.

13. A method of imaging a preselected antigen expressed in a mammal, said method comprising the steps of: (a) administering to said mammal at a concentration sufficient for extracorporeal detection of a said preselected antigen, a composition comprising a pharmaceutically acceptable carrier in combination with a dimeric biosynthetic construct that binds at least one preselected antigen, wherein the construct comprises two separate polypeptide chains, which have an amino acid sequence defining an sFv comprising two polypeptide domains connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each said sFv together defining a binding site immunologically reactive with a said preselected antigen, one of said polypeptide chains further comprising an amino acid sequence defining an N-terminal tail comprising at least one amino acid having a derivatizable amino acid side chain, and the other of said polypeptide chains further comprising an amino acid sequence defining a C-terminal tail comprising at least one amino acid having a derivatizable amino acid side chain; an sFv coupler linking together each said sFv through the derivatizable amino acid side chain disposed within the N-terminal tail of one polypeptide chain and the derivatizable amino acid side chain disposed within the C-terminal tail of the other polypeptide chain, said dimeric biosynthetic construct having a conformation wherein the binding site of each said sFv is operative to bind a said preselected antigen when said dimeric biosynthetic construct is administered to said mammal; and (b) detecting said dimeric biosynthetic construct bound to a said preselected antigen.

14. The method of claim 13, wherein said dimeric biosynthetic construct further comprises a detectable moiety.

15. The method of claim 14, wherein said detectable moiety comprises a radioactive atom.

16. The method of claim 15, wherein said detectable moiety comprises Technetium-99m.

17. The method of claim 13, for use in magnetic resonance imaging.

18. The method of claim 13, wherein said preselected antigen is c-erbB-2 or a c-erbB-2 related antigen.

19. The method of claim 1, wherein said dimeric biosynthetic construct is a homodimer.

20. The method of claim 7, wherein said dimeric biosynthetic construct is a homodimer.

21. The method of claim 13, wherein said dimeric biosynthetic construct is a homodimer.

L2 ANSWER 7 OF 7 USPATFULL on STN
96:60443 Biosynthetic binding proteins for immuno-targeting.
Huston, James S., Chestnut Hill, MA, United States
Houston, L. L., Oakland, CA, United States
Ring, David B., Redwood City, CA, United States
Oppermann, Hermann, Medway, MA, United States
Chiron Corporation, Emeryville, CA, United States (U.S. corporation)Creative BioMolecules, Inc., Hopkinton, MA, United States (U.S. corporation)

US 5534254 19960709
APPLICATION: US 1993-133804 19931007 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A composition for targeting an epitope on an antigen expressed in a mammal, wherein the composition comprises a pharmaceutically acceptable carrier in combination with, a dimeric biosynthetic construct for binding at least one preselected antigen, wherein the construct comprises: (a) two separate polypeptide chains, each of which have an amino acid sequence defining (1) an sFv comprising two polypeptide domains connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each said sFv together defining a binding site immunologically reactive with a said preselected antigen, and (2) a C-terminal tail essentially free of helical character under physiological conditions and comprising at least one amino acid having derivatizable amino acid side chain; and (b) an sFv coupler linking together each said sFv through the derivatizable amino acid side chain disposed within the C-terminal tail of each sFv, said dimeric construct having a conformation wherein the binding site of each said sFv binds a said preselected antigen when said dimeric construct is administered to said mammal.

2. A composition for targeting an epitope on an antigen expressed in a mammal, wherein the composition comprises a pharmaceutically acceptable carrier in combination with, a dimeric biosynthetic construct for binding to a preselected antigen, wherein the construct comprises: (a) two separate polypeptide chains, each of which have an amino acid sequence defining (1) an sFv comprising two polypeptide domains connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each said sFv together defining a binding site immunologically reactive with a said preselected antigen, and (2) a C-terminal tail essentially free of helical character under physiological conditions and comprising at least one amino acid having a derivatizable amino acid side chain; and (b) an sFv coupler linking together each said sFv through the derivatizable amino acid side chain disposed within the C-terminal tail of each sFv to form a homodimeric construct, said homodimeric construct having a conformation which binds said preselected antigen in said mammal with an avidity greater than the avidity of either sFv individually.

3. The composition of claim 1 or 2 wherein said C-terminal tail comprises the amino acid sequence Ser-Cys.

4. The composition of claim 1 or 2 wherein said C-terminal tail comprises the amino acid sequence $(Gly)_4$ -Cys (SEQ ID NO. 10).

5. The composition of claim 1 or 2 wherein said C-terminal tail comprises the amino acid sequence $(His)_6$ -$(Gly)_4$ -Cys (SEQ ID NO. 11).

6. The composition of claim 1 or 2 wherein said C-terminal tail chelates one or more ions.

7. The composition of claim 6 wherein said ion is a metal ion.

8. The composition of claim 1 or 2 wherein said amino acid having a derivatizable amino acid side chain is selected from the group consisting of lysine, arginine and histidine.

9. The composition of claim 1 or 2 wherein said amino acid having a derivatizable amino acid side chain is a cysteine amino acid.

10. The composition of claim 1 or 2 wherein said sFv coupler is a chemical bridge.

11. The composition of claim 1 or 2 wherein said linkage comprises a disulfide bond.

12. The composition of claim 1 or 2 wherein said linkage comprises a bismaleimidohexane cross-linker.

13. The composition of claim 1 or 2 wherein said linkage comprises a bismaleimidocaproyl amino acid linker.

14. The composition of claim 1 or 2 wherein said sFv coupler further comprises a detectable moiety.

15. The composition of claim 14 wherein said detectable moiety comprises Technetium-99m.

16. The composition of claim 14 wherein said detectable moiety comprises means for inducing proton relaxation in vivo.

17. The composition of claim 1 or 2 wherein said biosynthetic construct targets said epitope on said antigen with an avidity greater than that of a monoclonal antibody having the same antigenic determinant as said construct, or fragment thereof.

18. The composition of claim 1 or 2 wherein said biosynthetic construct targets said epitope on said antigen with an avidity greater than that of either sFv individually.

19. The composition of claim 1 or 2 wherein said preselected antigen is expressed on the surface of a cell.

20. The composition of claim 1 or 2 wherein said antigen is an intracellular component exposed upon cell lysis.

21. The composition of claim 1 wherein said biosynthetic construct binds two different epitopes.

22. The composition of claim 1 or 2 wherein said FR sequences are derived from a human immunoglobulin.

23. The composition of claim 1 or 2 wherein said CDR sequences are derived from an immunoglobulin that binds c-erbB-2 or a c-erbB-2 related antigen.

24. The composition of claim 23 wherein said CDR sequences are derived from an immunoglobulin selected from the group consisting of the monoclonal antibodies 520C9, 741F8, and 454C11.

25. The composition of claim 1 or 2 having the amino acid sequence found in SEQ ID NO. 1.

26. The composition of claim 1 or 2 wherein at least one of said polypeptide chains further comprises a detectable moiety.

27. The composition of claim 26 wherein said detectable moiety comprises a radioactive atom.

28. The composition of claim I or 2 wherein said biosynthetic construct remains localized to target tissue in a mammal for a longer time than either sFv individually.

29. A composition for targeting an epitope on an antigen expressed in a mammal, wherein the composition comprises a pharmaceutically acceptable carder in combination with, a dimeric biosynthetic construct for binding at least one preselected antigen, wherein the construct comprises: (a) two separate polypeptide chains, each of which have an amino acid sequence defining (1) an sFv comprising two polypeptide domains connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each said sFv together defining a binding site immunologically reactive with a said preselected antigen, and (2) an N-terminal tail comprising at least one amino acid having a derivatizable amino acid side chain; and (b) an sFv coupler linking together each said sFv through the derivatizable amino acid side chain disposed within the N-terminal tail of each sFv, said dimeric construct having a conformation wherein the binding site of each said sFv binds a preselected antigen when said dimeric construct is administered to said mammal.

30. A composition for targeting an epitope on an antigen expressed in a mammal, wherein the composition comprises a pharmaceutically acceptable carrier in combination with, a dimeric biosynthetic construct for binding at least one preselected antigen, wherein the construct comprises: (a) two separate polypeptide chains, wherein each of said polypeptide chains have amino acid sequence defining an sFv comprising two polypeptide domains connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each said domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each said sFv together defining a binding site immunologically reactive with a said preselected antigen, one of said polypeptide chains further comprising an amino acid sequence defining an N-terminal tail comprising at least one amino acid having a derivatizable amino acid side chain, and the other of said polypeptide chains further comprising an amino acid sequence defining a C-terminal tail comprising at least one amino acid having a derivatizable amino acid side chain; (b) an sFv coupler linking together each said sFv through the derivatizable amino acid side chain disposed within the N-terminal tail of one polypeptide chain and the derivatizable amino acid side chain disposed within the C-terminal tail of the other polypeptide chain, said dimeric construct having a conformation wherein the binding site of each said sFv binds a preselected antigen when said dimeric construct is administered to said mammal.

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E2         15     OPPERMANN GUNTER/AU
E3          0 --> OPPERMANN H/AU
E4          7     OPPERMANN HANS HERMANN/AU
E5          1     OPPERMANN HANS J/AU
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E7            2      OPPERMANN HARALD/AU
E8            1      OPPERMANN HEINZ/AU
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E10           1      OPPERMANN HENRY J/AU
E11           1      OPPERMANN HERALD/AU
E12           3      OPPERMANN HERMAN/AU

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E2            1      OPPERMANN HERALD/AU
E3            3  --> OPPERMANN HERMAN/AU
E4           94      OPPERMANN HERMANN/AU
E5            4      OPPERMANN HERRMANN/AU
E6            2      OPPERMANN HORST/AU
E7            1      OPPERMANN INGO/AU
E8            1      OPPERMANN JR KARL E/AU
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E12          14      OPPERMANN KLAUS GUNTER/AU

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             4 "OPPERMANN HERRMANN"/AU
L3         101 ("OPPERMANN HERMAN"/AU OR "OPPERMANN HERMANN"/AU OR "OPPERMANN
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L4          84 L3 NOT L1

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        367861 REGION?/CLM
           380 FRAMEWORK REGION?/CLM
                 ((FRAMEWORK(W)REGION?)/CLM)
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                                                   ENTRY    SESSION
FULL ESTIMATED COST                                25.44      25.65

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E7           4      HUSTON L A/IN
E8          14      HUSTON L B/IN
E9           1      HUSTON L G/IN
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        437716 REGION?
           365 FRAMEWORK REGION?
                 (FRAMEWORK(W)REGION?)
L7           9 L6 AND (FRAMEWORK REGION?)

=> d l7,bib,ab,1-9

L7   ANSWER 1 OF 9  WPIDS  COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN   2006-501905 [51]   WPIDS
CR   1988-353928 [49]; 1993-272889 [34]; 1996-333194 [33]; 1998-311318 [27];
     1999-023541 [02]; 2003-765156 [72]; 2005-222160 [23]
DNC  C2006-156783
TI   Formulation for targeting epitope on antigen expressed in mammal,
     comprises carrier in combination with dimeric biosynthetic construct for
     binding preselected antigen, and having two polypeptide chains, linker and
     crosslinking unit.
DC   B04 D16
IN   HOUSTON, L L; HUSTON, J S; OPPERMANN, H; RING, D B
PA   (HOUS-I) HOUSTON L L; (HUST-I) HUSTON J S; (OPPE-I) OPPERMANN H; (RING-I)
     RING D B
CYC  1
PI   US 2006147444   A1 20060706 (200651)*       31
ADT  US 2006147444 A1 CIP of US 1992-831967 19920206, Cont of US 1993-133804
     19931007, Cont of US 1995-462641 19950605, Cont of US 2000-558741
     20000426, US 2003-684237 20031010
FDT  US 2006147444 A1 Cont of US 5534254
PRAI US 1993-133804       19931007; US 1992-831967       19920206;
     US 1995-462641       19950605; US 2000-558741       20000426;
     US 2003-684237       20031010
AB   US2006147444 A UPAB: 20060809
     NOVELTY - A formulation for targeting an epitope on an antigen expressed
     in a mammal, comprises a carrier in combination with a dimeric
     biosynthetic construct for binding a preselected antigen, the construct
     comprising two polypeptide chains having amino acid sequences defining two
     polypeptide domains connected by a linker, a crosslinking unit and a
     linkage coupling the crosslinking unit on the polypeptide chains to form a
     homodimeric construct.
          DETAILED DESCRIPTION - A formulation (I) for targeting an epitope on
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an antigen expressed in a mammal, comprises a carrier in combination with, a dimeric biosynthetic construct for binding a preselected antigen, the construct comprising (a) two polypeptide chains, each of which have an amino acid sequence defining at least two polypeptide domains connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with the preselected antigen, and a C-terminal tail having a non-self-associating structure under physiological conditions and comprising a crosslinking unit, and (b) a linkage coupling the crosslinking unit on the two polypeptide chains to form a homodimeric construct, the homodimeric construct having a conformation permitting binding of the preselected antigen by the binding site of each of the polypeptide chain when administered to the mammal, where the binding avidity is greater than the avidity of either of the polypeptide chains individually.

An INDEPENDENT CLAIM is also included for a polypeptide chain (II) for binding preferentially to a preselected antigen, the polypeptide chain comprising an amino acid sequence defining at least two polypeptide domains connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each domain comprising CDRs interposed between FRs, the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with the preselected antigen, and a C-terminal tail having a non-self-associating structure under physiological conditions and comprising a crosslinking unit.

ACTIVITY - Cytostatic. No supporting data is given.

MECHANISM OF ACTION - None given.

USE - (I) is useful for targeting an epitope on an antigen expressed in a mammal (claimed). (I) is useful as in vivo imaging agents for ovarian and breast tumor tissue, and as diagnostic and therapeutic agents in diagnosis and treatment of malignancies.

ADVANTAGE - The dimeric construct of (I) has improved in vivo imaging characteristics, enhanced avidity in vivo (claimed). The dimeric construct has accelerated in vivo biodistribution and body clearance rates than that of antibodies or antibody fragments. The dimer biosynthetic constructs permit the in vivo targeting of an epitope on an antigen with greater apparent avidity including greater tumor specificity, tumor localization and tumor retention properties can that of Fab fragment having the same CDRs as the constructs.

Dwg.0/6

L7 ANSWER 2 OF 9 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 2005-222160 [23] WPIDS

CR 1988-353928 [49]; 1993-272889 [34]; 1996-333194 [33]; 1998-311318 [27]; 1999-023541 [02]; 2003-765156 [72]; 2006-501905 [51]

DNC C2005-071118

TI New isolated biosynthetic polypeptides comprising antigen binding sites, useful as diagnostic or therapeutic reagents for in vivo imaging and drug targeting experiments, or for diagnosing or treating tumors or malignancies.

DC B04 D16

IN **HUSTON, J S**; OPPERMANN, H

PA (HUST-I) HUSTON J S; (OPPE-I) OPPERMANN H

CYC 1

PI US 2005058638 A1 20050317 (200523)* 35

ADT US 2005058638 A1 Cont of US 1987-52800 19870521, Cont of US 1988-213671 19880630, CIP of US 1992-831967 19920206, Cont of US 1992-850228 19920312, Cont of US 1993-139901 19931019, CIP of US 1995-575724 19951218, CIP of US 2000-558741 20000426, US 2003-683547 20031010

FDT US 2005058638 A1 Cont of US 5132405, Cont of US 5476786, CIP of US 6207804
PRAI US 2003-683547 20031010; US 1987-52800 19870521;
US 1988-213671 19880630; US 1992-831967 19920206;
US 1992-850228 19920312; US 1993-139901 19931019;
US 1995-575724 19951218; US 2000-558741 20000426
AB US2005058638 A UPAB: 20060809
NOVELTY - An isolated polypeptide that includes an antigen-binding site, is new.

DETAILED DESCRIPTION - An isolated polypeptide comprises:

(a) two variable domain sequences, each variable domain sequence independently comprising at least one group of 3 complementarity determining regions (CDRs) interposed between **framework regions** (FRs), which variable domains are linked to a polypeptide linker to form a single polypeptide chain in which the FRs and CDRs together define a variable region binding domain which can be immunologically reactive with an antigen; and

(b) an amino acid sequence that is a part of the single polypeptide chain, and has a biological activity independent of the immunological reactivity.

ACTIVITY - Cytostatic.

No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The polypeptide is useful as a diagnostic or therapeutic reagent for in vivo imaging and drug targeting experiments. The polypeptide may be used for diagnosing or treating tumors or malignancies.
Dwg.0/8

L7 ANSWER 3 OF 9 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2003-765156 [72] WPIDS
CR 1988-353928 [49]; 1993-272889 [34]; 1996-333194 [33]; 1998-311318 [27]; 1999-023541 [02]; 2005-222160 [23]; 2006-501905 [51]
DNC C2003-209986
TI Novel binding protein formulation for targeting epitope on antigen in mammal, comprising dimeric biosynthetic construct having conformation permitting binding of antigen by binding site of each polypeptide chain.
DC B04 D16 K08
IN HOUSTON, L L; **HUSTON, J S**; OPPERMANN, H; RING, D B
PA (CHIR) CHIRON CORP
CYC 1
PI US 2002168375 A1 20021114 (200372)* 30
ADT US 2002168375 A1 CIP of US 1992-831967 19920206, Cont of US 1993-133804 19931007, Cont of US 1995-462641 19950605, Cont of US 2000-558741 20000426, US 2001-887853 20010621
FDT US 2002168375 A1 Cont of US 5534254
PRAI US 1993-133804 19931007; US 1992-831967 19920206;
US 1995-462641 19950605; US 2000-558741 20000426;
US 2001-887853 20010621
AB US2002168375 A UPAB: 20060809
NOVELTY - A formulation (I) for targeting an epitope on an antigen expressed in a mammal, comprising dimeric biosynthetic construct for binding at least one antigen having two polypeptide chains connected by a polypeptide linker, the dimeric construct having a conformation permitting binding of the antigen by the binding site of each polypeptide chain, is new.

DETAILED DESCRIPTION - A formulation (I) for targeting an epitope on an antigen expressed in a mammal, the formulation comprising a carrier in combination with a dimeric biosynthetic construct for binding at least one or preferentially to a preselected antigen, the construct comprising two polypeptide chains, each of which have an amino acid sequence defining at least two polypeptide domains, connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of

the other, the amino acid sequence of each domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with the preselected antigen, and a C-terminal tail having anon-self-associating structure under physiological conditions and comprising at least a crosslinking unit, and a linkage coupling the crosslinking unit on the two polypeptide chains, the dimeric construct having a conformation permitting binding of the preselected antigen by the binding site of each polypeptide chain when administered to the mammal or to form a homodimeric construct, the homodimeric construct having a conformation permitting binding to the preselected antigen in the mammal with an avidity greater than the avidity of either of the polypeptide chains individually.

INDEPENDENT CLAIMS are also included for:

(1) a polypeptide chain (II) for binding preferentially to a preselected antigen, comprising an amino acid sequence defining at least two polypeptide domains, connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each domain having CDRs interposed between FRs, the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with the preselected antigen, and a C-terminal tail having a non-self-associating structure under physiological conditions and comprising at least a cross-linking unit;

(2) a single-chain Fv (sFv) polypeptide (III) for binding preferentially to a c-erbB-2 or a c-erbB-2-related tumor antigen, comprising an amino acid sequence defining at least two polypeptide domains, connected by a polypeptide linker spanning the distance between the C-terminus of one domain and the N-terminus of the other, the amino acid sequence of each domain having CDRs interposed between FRs, the CDRs and FRs of each polypeptide chain together defining a binding site immunologically reactive with the c-erbB-2 or c-erbB-2-related tumor antigen;

(3) a DNA sequence (IV) encoding (I), (II) or (III); and

(4) a host cell transfected with (IV).

USE - (I) is useful for imaging a preselected antigen in a mammal expressing the antigen, involves administering to the mammal (I) having affinity for the preselected antigen at a concentration sufficient to permit extracorporeal detection of the construct bound to the preselected antigen, and detecting the polypeptide chain bound to the antigen, magnetic resonance imaging, in vivo imaging agent (claimed). (I) is useful for targeting drugs that inhibits cell proliferation and cytotoxic agents that kill cells.

ADVANTAGE - The biosynthetic construct is capable of remaining localized to target tissue in a mammal for a longer time than either of the polypeptide chains individually.

Dwg.0/6

L7 ANSWER 4 OF 9 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 1999-023541 [02] WPIDS
CR 1988-353928 [49]; 1993-272889 [34]; 1996-333194 [33]; 1998-311318 [27]; 2003-765156 [72]; 2005-222160 [23]; 2006-501905 [51]
DNC C1999-007187
TI Nucleic acid encoding single-chain Fv fragment specific for antigens - and having C-terminal tail for crosslinking to form dimer with improved pharmacokinetic properties, used to deliver drugs and imaging agents, especially to tumours.
DC B04 D16
IN HOUSTON, L L; **HUSTON, J S**; OPPERMANN, H; RING, D B
PA (CHIR) CHIRON CORP; (CREA-N) CREATIVE BIOMOLECULES INC
CYC 1
PI US 5837846 A 19981117 (199902)* 29

ADT US 5837846 A CIP of US 1992-831967 19920206, Div ex US 1993-133804 19931007, US 1995-461386 19950605
FDT US 5837846 A Div ex US 5534254
PRAI US 1993-133804 19931007; US 1992-831967 19920206; US 1995-461386 19950605
AB US 5837846 A UPAB: 20060809
New isolated nucleic acid (I) encodes a polypeptide (II) that binds preferentially to a selected antigen (Ag). The polypeptide chain comprises:

(a) a single-chain Fv fragment (III) with two domains, each comprising complementarity determining regions (CDRs) between **framework regions** (FRs), connected by a peptide linker, the CDRs and FRs together defining a binding site for Ag (where the CDR regions are preferably derived from monoclonal antibodies 520C9, 741F8, or 454C11); and

(b) a C-terminal tail of Ser-Cys; (Gly)4-Cys; or (His)6-(Gly)4-Cys.

Also new are host cells transfected with (I).

USE - (I) are used to express (II), dimers of which are used for targeted delivery of drugs or imaging agents (e.g. cytotoxins, prodrugs or 99m-technetium) to Ag-expressing cells, particularly for treatment or diagnosis of tumours (especially of ovary or breast).

ADVANTAGE - Dimers of (II) have faster in vivo bio-distribution and body clearance than antibodies (or their fragments). They also have higher in vivo avidity (including target specificity and retention).

Dwg.0/6

L7 ANSWER 5 OF 9 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 1998-311318 [27] WPIDS
CR 1988-353928 [49]; 1993-272889 [34]; 1996-333194 [33]; 1999-023541 [02]; 2003-765156 [72]; 2005-222160 [23]; 2006-501905 [51]
DNC C1998-095897
TI Imaging of antigens in vivo - using dimers of single-chain antibody Fv fragments.
DC B04 D16 K08
IN HOUSTON, L L; **HUSTON, J S**; OPPERMANN, H; RING, D B
PA (CHIR) CHIRON CORP; (CREA-N) CREATIVE BIOMOLECULES INC
CYC 1
PI US 5753204 A 19980519 (199827)* 30
ADT US 5753204 A CIP of US 1992-831967 19920206, Div ex US 1993-133804 19931007, US 1995-461838 19950605
FDT US 5753204 A Div ex US 5534254
PRAI US 1993-133804 19931007; US 1992-831967 19920206; US 1995-461838 19950605
AB US 5753204 A UPAB: 20060809
A method (A) of imaging a preselected antigen expressed in a mammal, comprises: (a) administering to the mammal at a concentration sufficient for extracorporeal detection of the preselected antigen, a composition comprising a pharmaceutically acceptable carrier in combination with a dimeric biosynthetic construct that binds at least one preselected antigen, where the construct comprises two separate polypeptide chains, each of which has an amino acid sequence defining a single chain Fv (sFv) comprising two polypeptide domains connected by a polypeptide linker spanning the distance between the C terminus of one domain and the N terminus of the other, the amino acid sequence of each domain comprising complementarity determining regions (CDRs) interposed between **framework regions** (FRs), the CDRs and FRs of each sFv together defining a binding site immunologically reactive with a preselected antigen, and a C terminal tail essentially free of helical character under physiological conditions and comprising at least one amino acid having a derivatisable amino acid side chain, and an sFv coupler linking together each sFv through the derivatisable amino acid side chain disposed within the C terminal tail of each sFv, the dimeric biosynthetic construct having a conformation where

the binding site of each sFv is operative to bind a preselected antigen when the dimeric biosynthetic construct is administered to the mammal; and (b) detecting the dimeric biosynthetic construct bound to a preselected antigen. Also claimed is a method (B) of imaging a preselected antigen expressed in a mammal, comprising: (a) administering to the mammal at a concentration sufficient for extracorporeal detection of a preselected antigen a composition comprising a pharmaceutically acceptable carrier in combination with a dimeric biosynthetic construct that binds at least one preselected antigen, where the construct comprises two separate polypeptide chains, each of which has an amino acid sequence defining an sFv comprising two polypeptide domains connected by a polypeptide linker spanning the distance between the C terminus of one domain and the N terminus of the other, the amino acid sequence of each domain comprising CDRs interposed between FRs, the CDRs and FRs of each sFv together defining a binding site immunologically reactive with a preselected antigen, and an N terminal tail comprising at least one amino acid having a derivatisable amino acid side chain, and an sFv coupler linking together each sFv through the derivatisable amino acid side chain disposed within the N terminal tail of each sFv, the dimeric biosynthetic construct having a conformation where the binding site of each sFv is operative to bind a preselected antigen when the dimeric biosynthetic construct is administered to the mammal; and (b) detecting the dimeric biosynthetic construct bound to a preselected antigen. Also claimed is a method (C) of imaging a preselected antigen expressed in a mammal, comprising: (a) administering to the mammal at a concentration sufficient for extracorporeal detection of a preselected antigen, a composition comprising a pharmaceutically acceptable carrier in combination with a dimeric biosynthetic construct that binds at least one preselected antigen, where the construct comprises two separate polypeptide chains, which have an amino acid sequence defining an sFv comprising two polypeptide domains connected by a polypeptide linker spanning the distance between the C terminus of one domain and the N terminus of the other, the amino acid sequence of each domain comprising CDRs interposed between FRs, the CDRs and FRs of each sFv together defining a binding site immunologically reactive with a preselected antigen, one of the polypeptide chains further comprising an amino acid sequence defining an N terminal tail comprising at least one amino acid having a derivatisable amino acid side chain, and the other of the polypeptide chains further comprising an amino acid sequence defining a C terminal tail comprising at least one amino acid having a derivatisable amino acid side chain; an sFv coupler linking together each sFv through the derivatisable amino acid side chain disposed within the N terminal tail of one polypeptide chain and the derivatisable amino acid side chain disposed within the C terminal tail of the other polypeptide chain, the dimeric biosynthetic construct having a conformation where the binding site of each sFv is operative to bind a preselected antigen when the dimeric biosynthetic construct is administered to the mammal; and (b) detecting the dimeric biosynthetic construct bound to a preselected antigen.

USE - The method is for use in magnetic resonance imaging of c-erbB-2 or related antigens in cancer diagnosis.

ADVANTAGE - The biosynthetic constructs have enhanced properties as I(in vivo)I targetting agents in comparison with intact monoclonal antibodies or their Fab fragments. The dimeric constructs permit the I(in vivo)I targetting of an epitope on an antigen with greater apparent avidity, including greater tumour specificity, tumour localisation and tumour retention properties than that of the Fab fragment having the same CDRS as the construct.

Dwg.0/6

L7 ANSWER 6 OF 9 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 1996-333194 [33] WPIDS

CR 1988-353928 [49]; 1993-272889 [34]; 1998-311318 [27]; 1999-023541 [02]; 2003-765156 [72]; 2005-222160 [23]; 2006-501905 [51]
DNC C1996-105206
TI Compsns. contg. antigen-targetting antibody fragment constructs - comprising dimer of single-chain Fv fragments.
DC B04 D16 K08
IN HOUSTON, L L; **HUSTON, J S**; OPPERMANN, H; RING, D B
PA (CHIR) CHIRON CORP; (CREA-N) CREATIVE BIOMOLECULES INC
CYC 1
PI US 5534254 A 19960709 (199633)* 30
ADT US 5534254 A CIP of US 1992-831967 19920206, US 1993-133804 19931007
PRAI US 1993-133804 19931007; US 1992-831967 19920206
AB US 5534254 A UPAB: 20060809
Compsns. for targeting an epitope on an antigen expressed in a mammal comprise a carrier and a dimer comprising two single-chain antibody Fv (sFv) fragments linked together via a coupler. Each sFV fragment comprises (a) two antigen-binding domains connected by a polypeptide linker and (b) a tail that is non-helical under physiological conditions and comprises at least one amino acid with a derivatisable side chain. Each antigen-binding domain comprises complementarity-determining regions (CDRs) interposed between **framework regions** (FRs). The coupler links the two sFV fragments through the derivatisable side chains in their tails. Three major embodiments are claimed: (1) both sFv fragments have C-terminal tails that are non-helical under physiological conditions; (2) both sFv fragments have N-terminal tails; (3) one sFv fragment has an N-terminal tail and the other has a C-terminal tail.
USE - The compsns. are useful for in vivo imaging and drug-targeting experiments.
ADVANTAGE - Homodimers in which both sFv fragments target the same antigen have greater binding avidity than the individual sFv fragments, giving longer tissue retention times.
Dwg.0/6

L7 ANSWER 7 OF 9 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 1993-386569 [48] WPIDS
DNN N1993-298487 DNC C1993-171985
TI Chimeric multivalent protein analogues - useful for diagnostic imaging and cytotoxic therapy.
DC B04 D16 S03
IN **HUSTON, J S**; KECK, P C
PA (CREA-N) CREATIVE BIOMOLECULES; (CREA-N) CREATIVE BIOMOLECULES INC
CYC 43
PI WO 9323537 A1 19931125 (199348)* EN 106
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE
W: AT AU BB BG BR CA CH CZ DE DK ES FI GB HU JP KP KR LK LU MG MN MW NL NO NZ PL PT RO RU SD SE SK UA US VN
AU 9342389 A 19931213 (199413)
EP 640130 A1 19950301 (199513) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
AU 675223 B 19970130 (199713)
EP 640130 B1 19980415 (199819) EN 65
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
DE 69318016 E 19980520 (199826)
ADT WO 9323537 A1 WO 1993-US4338 19930507; AU 9342389 A AU 1993-42389 19930507; EP 640130 A1 EP 1993-911146 19930507, WO 1993-US4338 19930507; AU 675223 B AU 1993-42389 19930507; EP 640130 B1 EP 1993-911146 19930507, WO 1993-US4338 19930507; DE 69318016 E DE 1993-618016 19930507, EP 1993-911146 19930507, WO 1993-US4338 19930507
FDT AU 9342389 A Based on WO 9323537; EP 640130 A1 Based on WO 9323537; AU 675223 B Previous Publ. AU 9342389, Based on WO 9323537; EP 640130 B1 Based on WO 9323537; DE 69318016 E Based on EP 640130, Based on WO 9323537

PRAI US 1992-881109 19920508
AB WO 9323537 A UPAB: 19940120
A chimeric multivalent immunoglobulin (Ig) superfamily protein analogue (A) comprises (a) one or more polypeptide chains-forming a beta-barrel domain-contg. complementary-determining region (CRD)-like portions and **framework region** (Fr)-like portions; and (b) 2 or more ligand binding site (LBS) segments spliced into the Fr-like regions of the beta-barrel domain. The core-like regions define a ligand binding site.

Also claimed are: (1) biological material having a nucleotide sequence (I), encloding (A); (2) a replicable recombinant DNA expression vector, contg. (I); (3) a polylinker and bridge contained within (A), (4) a method for producing (A), comprising: (a) determining splice points for CDR-like regions to form additional LBS segments on the FR-like regions of a beta-barrel domain; (b) determining the sequence of the resultant construct having 2 LB S segments; (c) deducing the DNA sequence of the construct; (d) synthesising the DNA sequence; (e) inserting the DNA sequence into an appropriate expression vector and expressing (A) in a suitable host system; (f) isolating and purifying (A); and (g) refolding purified (A) to its immunologically reactive conformation, resulting in a chimeric, multivalent Ig superfamily protein analogue; and (5) a molecular switch comprising (A).

USE - (A) is useful in a pharmaceutical composition for imaging specific tissue in a host, irradiating specific tissue in a host, delivering a cytotoxic substance to specific host tissue, lysing target cells in hosts having cytotoxic cells, modifying cell surfae receptor function and effecting cell-cell interactions.
Dwg.0/17

L7 ANSWER 8 OF 9 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 1993-272889 [34] WPIDS
CR 1988-353928 [49]; 1996-333194 [33]; 1998-311318 [27]; 1999-023541 [02]; 2003-765156 [72]; 2005-222160 [23]; 2006-501905 [51]
DNN N1993-209536 DNC C1993-121786
TI New single chain Fv polypeptide binding to C-erbB-2 tumour antigen - for imaging or treating breast or ovarian cancer etc..
DC B04 D16 S03
IN HOUSTON, L L; **HUSTON, J S**; OPPERMANN, H; RING, D B; HOUSTON, L; HUSTON, S; RING, B
PA (CHIR) CHIRON CORP; (CREA-N) CREATIVE BIOMOLECULES INC; (CURI-N) CURIS INC; (CETU) CETUS ONCOLOGY CORP
CYC 21
PI WO 9316185 A2 19930819 (199334)* 87
RW: BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
W: AU CA JP
AU 9336122 A 19930903 (199401)
EP 625200 A1 19941123 (199445) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
WO 9316185 A3 19930930 (199513)
JP 08500962 W 19960206 (199643) 91
AU 675929 B 19970227 (199717)
US 5877305 A 19990302 (199916)
CA 2372813 A1 19930819 (200237) EN
JP 2003284577 A 20031007 (200367) 49
EP 1514934 A2 20050316 (200519) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 2005104965 A 20050421 (200527) 59
EP 625200 B1 20050511 (200536) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
DE 69333807 E 20050616 (200540)
JP 2005168489 A 20050630 (200543) 59
CA 2129663 C 20050705 (200545) EN

DE 69333807 T2 20060202 (200612)

ADT WO 9316185 A2 WO 1993-US1055 19930205; AU 9336122 A AU 1993-36122 19930205; EP 625200 A1 EP 1993-904938 19930205, WO 1993-US1055 19930205; WO 9316185 A3 WO 1993-US1055 19930205; JP 08500962 W JP 1993-514197 19930205, WO 1993-US1055 19930205; AU 675929 B AU 1993-36122 19930205; US 5877305 A Cont of US 1992-831967 19920206, US 1994-356786 19941212; CA 2372813 A1 Div ex CA 1993-2129663 19930205, CA 1993-2372813 19930205; JP 2003284577 A Div ex JP 1993-514197 19930205, JP 2003-81465 19930205; EP 1514934 A2 Div ex EP 1993-904938 19930205, EP 2004-78206 19930205; JP 2005104965 A Div ex JP 1993-514197 19930205, JP 2004-178961 20040616; EP 625200 B1 EP 1993-904938 19930205, WO 1993-US1055 19930205, Related to EP 2004-78206 20041124; DE 69333807 E DE 1993-633807 19930205, EP 1993-904938 19930205, WO 1993-US1055 19930205; JP 2005168489 A Div ex JP 2003-81465 19930205, JP 2004-260280 20040907; CA 2129663 C CA 1993-2129663 19930205, WO 1993-US1055 19930205; DE 69333807 T2 DE 1993-633807 19930205, EP 1993-904938 19930205, WO 1993-US1055 19930205

FDT AU 9336122 A Based on WO 9316185; EP 625200 A1 Based on WO 9316185; JP 08500962 W Based on WO 9316185; AU 675929 B Previous Publ. AU 9336122, Based on WO 9316185; EP 1514934 A2 Div ex EP 625200; EP 625200 B1 Related to EP 1514934, Based on WO 9316185; DE 69333807 E Based on EP 625200, Based on WO 9316185; CA 2129663 C Based on WO 9316185; DE 69333807 T2 Based on EP 625200, Based on WO 9316185

PRAI US 1992-831967 19920206; US 1994-356786 19941212

AB WO 9316185 A UPAB: 20060809

New single chain Fv polypeptide (I) defines a binding state having the binding properties of an immunoglobulin able to bind c-erbB-2 (or related) tumour antigens. (I) contains at least 2 polypeptide domains (PPD) connected by a polypeptide linker (between the C terminus of one domain and the N terminus of the other). Each PPD comprises a set of complementarity determining regions (CDR) providing binding to the antigen, interspersed between a set of **framework regions** (FR).

Also new are (1) DNA encoding (I) and (2) host cells transfected with such DNA.

Opt. (I) is coupled to a detectable residue or to a toxin.

USE/ADVANTAGE - (I) can be used to image cells carrying the specified antigen when coupled to detectable gp. or, when coupled to a toxin or radioisotope, for treatment of tumours which express this antigen (e.g. breast or ovarian cancers). Compared with complete antibodies (or their larger fragments), (I) are less susceptible to proteolysis; reach their target (and are cleaned) more rapidly, and have lower non-specific binding and immunogenicity. Some (I) also cause internalisation of the antigen and (I)-toxin fusion proteins have 15-200 times greater tumour cell killing activity than chemically crosslinked toxin/whole antibody (or Fab) constructs. (I) can also be used (not claimed) in specific binding assays; affinity purificn. and as biocatalysts. Where (I) contains a second binding site specific for CD3, it may also induce antibody-dependent cell cytotoxicity.

Dwg.1/4

L7 ANSWER 9 OF 9 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 1988-353928 [49] WPIDS

CR 1993-272889 [34]; 1996-333194 [33]; 1998-311318 [27]; 1999-023541 [02]; 2003-765156 [72]; 2005-222160 [23]; 2006-501905 [51]

DNC C1988-156568

TI Recombinant multifunctional protein - having an antibody binding site and a sequence for biological activity, ion sequestering or binding to a solid support.

DC B04 D16

IN **HUSTON, J S**; OPPERMANN, H; HUSTON, J

PA (CREA-N) CREATIVE BIOMOLECULES INC; (MICR-N) MICROMET AG; (CURI-N) CURIS INC

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CYC  18
PI   WO 8809344       A  19881201 (198849)* EN  115
        RW: AT BE CH DE FR GB IT LU NL SE
         W: AU DK FI JP NO US
     AU 8818049       A  19881221 (198916)
     EP 318554        A  19890607 (198923)  EN
         R: AT BE CH DE FR GB IT LI LU NL SE
     JP 02500329      W  19900208 (199012)
     US 5091513       A  19920225 (199211)       36
     AU 9185799       A  19920213 (199217)
     US 5132405       A  19920721 (199232)       33
     US 5258498       A  19931102 (199345)       67
     AU 648591        B  19940428 (199422)
     EP 623679        A1 19941109 (199443)  EN   56
         R: AT BE CH DE FR GB IT LI LU NL SE
     EP 318554        A4 19900314 (199511)
     EP 318554        B1 19950405 (199518)  EN   58
         R: AT BE CH DE FR GB IT LI LU NL SE
     DE 3853515       G  19950511 (199524)
     US 5476786       A  19951219 (199605)       34
     US 5482858       A  19960109 (199608)       67
     US 6207804       B1 20010327 (200129)       26
     CA 1341415       C  20030107 (200307)  EN
     EP 623679        B1 20030625 (200349)  EN
         R: AT BE CH DE FR GB IT LI LU NL SE
     DE 3856559       G  20030731 (200353)
     EP 318554        B2 20050112 (200505)  EN
         R: AT BE CH DE FR GB IT LI LU NL SE
ADT  WO 8809344 A WO 1988-US1737 19880519; EP 318554 A EP 1988-905298 19880519;
     JP 02500329 W JP 1988-505025 19880519; US 5091513 A US 1991-636765
     19910102; US 5132405 A Cont of US 1987-52800 19870521, US 1988-213671
     19880630; US 5258498 A CIP of US 1987-52800 19870521, WO 1988-US1737
     19880519, Cont of US 1989-342449 19890123, US 1989-955399 19890123; AU
     648591 B AU 1991-85799 19911011, Div ex AU 1988-18049          ; EP 623679
     A1 Related to EP 1988-905298 19880519, EP 1994-201816 19880519; EP 318554
     A4 EP 1988-905298          ; EP 318554 B1 EP 1988-905298 19880519, WO
     1988-US1737 19880519; DE 3853515 G DE 1988-3853515 19880519, EP
     1988-905298 19880519, WO 1988-US1737 19880519; US 5476786 A Cont of US
     1987-52800 19870521, Cont of US 1988-213761 19880630, Cont of US
     1992-850228 19920312, US 1993-139901 19931019; US 5482858 A CIP of US
     1987-52800 19870521, Cont of US 1989-342449 19890123, Cont of US
     1992-955399 19921001, US 1993-139171 19931019; US 6207804 B1 Cont of US
     1987-52800 19870521, Cont of US 1988-213671 19880630, Cont of US
     1992-850228 19920312, Cont of US 1993-139901 19931019, US 1995-575724
     19951218; CA 1341415 C CA 1988-567480 19880520; EP 623679 B1 Div ex EP
     1988-905298 19880519, EP 1994-201816 19880519; DE 3856559 G DE
     1988-3856559 19880519, EP 1994-201816 19880519; EP 318554 B2 EP
     1988-905298 19880519, WO 1988-US1737 19880519, Related to EP 1994-201816
     19880519
FDT  US 5258498 A Based on WO 8809344; AU 648591 B Previous Publ. AU 9185799;
     EP 318554 B1 Based on WO 8809344; DE 3853515 G Based on EP 318554, Based
     on WO 8809344; US 5476786 A Cont of US 5132405; US 5482858 A Cont of US
     5258498; US 6207804 B1 Cont of US 5132405, Cont of US 5476786; EP 623679
     B1 Div ex EP 318554; DE 3856559 G Based on EP 623679; EP 318554 B2 Related
     to EP 623679, Based on WO 8809344
PRAI US 1987-52800        19870521; US 1988-213761       19880630;
     US 1991-636765       19910102; US 1988-213671       19880630;
     US 1989-342449       19890123; US 1989-955399       19890123;
     US 1992-850228       19920312; US 1993-139901       19931019;
     US 1992-955399       19921001; US 1993-139171       19931019;
     US 1995-575724       19951218
AB   WO   8809344 A UPAB: 20060809
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A single chain multi-functional biosynthetic protein expressed from a single gene derived by recombinant DNA techniques is claimed, the protein comprising (a) a biosynthetic antibody binding site capable of binding to a preselected antigenic determinant and comprising at least one protein domain, the amino acid sequence of the domain being homologous to at least a portion of the sequence of a variable region of an immunoglobulin molecule capable of binding the preselected antigenic determine and, peptide bonded to this (b) a polypeptide selected from effector proteins having a conformation suitable biological activity in mammals, amino acid sequences capable of sequestering an ion and amino acid sequences capable of selective binding to a solid support.

The effector protein may be e.g. an enzyme, toxin, receptor, binding site, growth factor, lymphokine, cytokine anti-metabolite. The sequence capable of sequestering an ion may be e.g. calmodulin or metallothionein. The sequence capable of binding to a solid support is e.g. streptavidin or a fragment of protein A.

USE/ADVANTAGE - The proteins may be used for e.g. specific binding assays, affinity purificn., biocatalysts, drug targeting, imaging and immunological treatment of oncogenid and infectious diseases. They offer fewer cleavage sites to circulating proteolytic enzymes and have improved stability. They reach their target tissue rapidly and are cleared quickly from the body. They also have reduced immunogenicity. Their design facilitates coupling to other moieties in drug targeting and imaging applications.

Dwg.0/15

```
=> e oppermann h/in
E1            1     OPPERMANN F B/IN
E2           58     OPPERMANN G/IN
E3          138 --> OPPERMANN H/IN
E4            2     OPPERMANN H A/IN
E5            2     OPPERMANN H H/IN
E6            1     OPPERMANN H J/IN
E7            1     OPPERMANN H R/IN
E8            1     OPPERMANN H U/IN
E9            6     OPPERMANN I/IN
E10           1     OPPERMANN I J/IN
E11           3     OPPERMANN J/IN
E12          48     OPPERMANN K/IN

=> s e3
L8          138 "OPPERMANN H"/IN

=> d his

     (FILE 'HOME' ENTERED AT 20:15:09 ON 27 SEP 2006)

     FILE 'USPATFULL' ENTERED AT 20:15:17 ON 27 SEP 2006
                E HUSTON JAMES S/IN
L1           26 S E3
L2            7 S L1 AND (FRAMEWORK REGION?/CLM)
                E OPPERMANN H/AU
                E E12
L3          101 S E3-E5
L4           84 S L3 NOT L1
L5            0 S L4 AND (FRAMEWORK REGION?/CLM)

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L6           20 S E3
L7            9 S L6 AND (FRAMEWORK REGION?)
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            E OPPERMANN H/IN
L8          138 S E3

=> s l8 not l6
L9          126 L8 NOT L6

=> s l9 and (framework region?)
         31820 FRAMEWORK
        437716 REGION?
           365 FRAMEWORK REGION?
                 (FRAMEWORK(W)REGION?)
L10           0 L9 AND (FRAMEWORK REGION?)

=> file medline
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               60.63      86.28

FILE 'MEDLINE' ENTERED AT 20:23:24 ON 27 SEP 2006

 FILE LAST UPDATED: 27 Sep 2006 (20060927/UP). FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available. For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> e huston j s/au
E1          248     HUSTON J P/AU
E2            8     HUSTON J R/AU
E3           35 --> HUSTON J S/AU
E4            1     HUSTON J T/AU
E5            8     HUSTON J W/AU
E6            1     HUSTON J W 3RD/AU
E7            3     HUSTON JAMES S/AU
E8            5     HUSTON JANIS L/AU
E9            1     HUSTON JARED/AU
E10           4     HUSTON JARED M/AU
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E12           2     HUSTON JOHN/AU

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L11          35 "HUSTON J S"/AU

=> s l11 and (framework region?)
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        802979 REGION?
           415 FRAMEWORK REGION?
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=> d l11,ti,1-10

L11  ANSWER 1 OF 35      MEDLINE on STN
TI   Engineered antibodies take center stage.

L11  ANSWER 2 OF 35      MEDLINE on STN
TI   Human single-chain Fv intrabodies counteract in situ huntingtin
     aggregation in cellular models of Huntington's disease.

L11  ANSWER 3 OF 35      MEDLINE on STN
TI   Extended half-life and elevated steady-state level of a single-chain Fv
     intrabody are critical for specific intracellular retargeting of its
     antigen, caspase-7.

L11  ANSWER 4 OF 35      MEDLINE on STN
TI   Exploring and exploiting the antibody and Ig superfamily combining sites.

L11  ANSWER 5 OF 35      MEDLINE on STN
TI   In vitro and in vivo characterization of a human anti-c-erbB-2
     single-chain Fv isolated from a filamentous phage antibody library.

L11  ANSWER 6 OF 35      MEDLINE on STN
TI   An overview of the 1996 Keystone meeting. Exploring and exploiting
     antibody and Ig superfamily combining sites.

L11  ANSWER 7 OF 35      MEDLINE on STN
TI   Single-chain Fv radioimmunotargeting.

L11  ANSWER 8 OF 35      MEDLINE on STN
TI   Antibody binding sites.

L11  ANSWER 9 OF 35      MEDLINE on STN
TI   Symmetry of Fv architecture is conducive to grafting a second antibody
     binding site in the Fv region.

L11  ANSWER 10 OF 35     MEDLINE on STN
TI   Enhanced tumor specificity of 741F8-1 (sFv')2, an anti-c-erbB-2
     single-chain Fv dimer, mediated by stable radioiodine conjugation.


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L11  ANSWER 1 OF 35      MEDLINE on STN
2002182647.    PubMed ID: 11847424.   Engineered antibodies take center stage.
     Huston J S; George A J. (Lexigen Pharmaceuticals Corp, 125 Hartwell
     Avenue, Lexington, MA 02421-3125, USA.. jhuston@lexigenpharm.com) . Human
     antibodies, (2001) Vol. 10, No. 3-4, pp. 127-42.  Ref: 174. Journal code:
     9711270. ISSN: 1093-2607. Pub. country: Netherlands. Language: English.
AB   The start of the post-genomic era provides a useful juncture for
     reflection on the state of antibody engineering, which will be a critical
     technology for relating function and pathology to genomic sequence in
     biology and medicine. The phenomenal progress in deciphering the human
     genome has given significant impetus to the application of engineered
     antibodies in proteomics. Thus, advances in phage display antibody
     libraries can now help to define novel gene function and the measurement
     of abnormal protein expression in pathological states. Furthermore,
     intrabody and antibody engineering provide vehicles for the development of
     molecular medicines of the future. In addition to these new directions,
     antibody engineering has begun to show concrete success in its long-term
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efforts to develop targeted immunotherapies for cancer and other diseases. The cornerstones of clinical development are the detailed academic clinical trials that continue to push the boundaries of engineered antibodies into the real world. The field displays a healthy impatience for practical results, as research accelerates with concerted efforts to transfer preclinical insights into clinical trials. Growing private and governmental expenditures will lead to the rapid expansion of life-saving immunotherapeutic agents. The present review developed from our effort to report on the 11th Annual International Conference on Antibody Engineering (3-6 December 2000). This annual meeting is a forum for discussions on the latest advances in antibody engineering groups from around the world, and now includes the broader agenda of engineering in molecular immunology. In bringing scientists together to exchange ideas at this open forum, new collaborations and the threads of new discoveries are woven. For example, Professors Gerhard Wagner (Harvard Medical School), Dennis Burton (Scripps Research Institute), and Peter Hudson (CSIRO, Melbourne, Australia) gave exciting insights on structural immunobiology that had implications across many disciplines. The growth in antibody engineering was highlighted by the attendance of some 600 participants at the meeting, doubling that of the 1999 meeting. Dramatic clinical acceptance of monoclonal antibodies during the past two years has fostered this growth, with sales in 2000 of 1.8 billion dollars and projections for 2001 of 3 billion dollars. However, economic measures cannot begin to convey the medical revolution that is being effected by these first humanized and chimerized monoclonal antibodies. At this juncture, the 10 monoclonal antibody therapeutics in clinical use are of murine origin, of which 3 are entirely murine (OKT3, Mylotarg, 90Y-labeled Bexxar), 4 have been chimerized (human constant domains replacing murine) (ReoPro, Rituxan and its 131I-labeled analogue (Zevalin), Simulect, Remicade) and 3 were chimerized and humanized (human residues being substituted for at least some mouse-specific framework residues in VH and VL) (Zenapax, Herceptin, Synagis). Fully humanized anti-CD52 (CAMPATH-1H) has also been approved by the FDA for the treatment of B-cell chronic lymphocytic leukemia and should become available in late 2001. Humanization was initially developed by Dr. Greg Winter at the MRC Laboratory of Molecular Biology (Cambridge, UK), who presented the meeting's keynote address, "Antibodies as a Paradigm for Molecular Evolution". His pioneering work in antibody phage display libraries has been reformulated into a daring approach to develop truly novel proteins with genetically paired structural elements. He described studies in combinatorial protein engineering with enormous implications for both industrial and therapeutic applications of macromolecules.

L11 ANSWER 2 OF 35 MEDLINE on STN

2001220559. PubMed ID: 11296304. Human single-chain Fv intrabodies counteract in situ huntingtin aggregation in cellular models of Huntington's disease. Lecerf J M; Shirley T L; Zhu Q; Kazantsev A; Amersdorfer P; Housman D E; Messer A; **Huston J S**. (IntraImmune Therapies, Inc., Lexington, MA 02215, USA.) Proceedings of the National Academy of Sciences of the United States of America, (2001 Apr 10) Vol. 98, No. 8, pp. 4764-9. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB This investigation was pursued to test the use of intracellular antibodies (intrabodies) as a means of blocking the pathogenesis of Huntington's disease (HD). HD is characterized by abnormally elongated polyglutamine near the N terminus of the huntingtin protein, which induces pathological protein-protein interactions and aggregate formation by huntingtin or its exon 1-containing fragments. Selection from a large human phage display library yielded a single-chain Fv (sFv) antibody specific for the 17 N-terminal residues of huntingtin, adjacent to the polyglutamine in HD exon 1. This anti-huntingtin sFv intrabody was tested in a cellular model of the disease in which huntingtin exon 1 had been fused to green

fluorescent protein (GFP). Expression of expanded repeat HD-polyQ-GFP in transfected cells shows perinuclear aggregation similar to human HD pathology, which worsens with increasing polyglutamine length; the number of aggregates in these transfected cells provided a quantifiable model of HD for this study. Coexpression of anti-huntingtin sFv intrabodies with the abnormal huntingtin-GFP fusion protein dramatically reduced the number of aggregates, compared with controls lacking the intrabody. Anti-huntingtin sFv fused with a nuclear localization signal retargeted huntingtin analogues to cell nuclei, providing further evidence of the anti-huntingtin sFv specificity and of its capacity to redirect the subcellular localization of exon 1. This study suggests that intrabody-mediated modulation of abnormal neuronal proteins may contribute to the treatment of neurodegenerative diseases such as HD, Alzheimer's, Parkinson's, prion disease, and the spinocerebellar ataxias.

L11 ANSWER 3 OF 35 MEDLINE on STN

2000115641. PubMed ID: 10648939. Extended half-life and elevated steady-state level of a single-chain Fv intrabody are critical for specific intracellular retargeting of its antigen, caspase-7. Zhu Q; Zeng C; Huhalov A; Yao J; Turi T G; Danley D; Hynes T; Cong Y; DiMattia D; Kennedy S; Daumy G; Schaeffer E; Marasco W A; **Huston J S**. (IntraImmune Therapies Inc., P.O. Box 15599, Boston, MA 02215-0011,. USA.quanzhu@tiac.net) . Journal of immunological methods, (1999 Dec 10) Vol. 231, No. 1-2, pp. 207-22. Journal code: 1305440. ISSN: 0022-1759. Pub. country: Netherlands. Language: English.

AB 8 h) and high steady-state levels of protein accumulation, while the H2 intrabodies had a half-life of 2 h and less protein at steady state. These results suggest that the choice of sFv as an intrabody depends critically on the intracellular sFv protein having an extended half-life and elevated steady-state level. Thus, extended half-life must be considered together with sFv antibody specificity and affinity when choosing an optimal sFv intrabody for functional studies of cellular proteins.

L11 ANSWER 4 OF 35 MEDLINE on STN

1998294402. PubMed ID: 9630946. Exploring and exploiting the antibody and Ig superfamily combining sites. George A; **Huston J S**; Haber E. Nature biotechnology, (1996 May) Vol. 14, No. 5, pp. 584. Journal code: 9604648. ISSN: 1087-0156. Pub. country: United States. Language: English.

L11 ANSWER 5 OF 35 MEDLINE on STN

1998040666. PubMed ID: 9373335. In vitro and in vivo characterization of a human anti-c-erbB-2 single-chain Fv isolated from a filamentous phage antibody library. Schier R; Marks J D; Wolf E J; Apell G; Wong C; McCartney J E; Bookman M A; **Huston J S**; Houston L L; Weiner L M; +. (Department of Anesthesia and Pharmaceutical Chemistry, University of California, San Francisco, USA.) Immunotechnology : an international journal of immunological engineering, (1995 May) Vol. 1, No. 1, pp. 73-81. Journal code: 9511979. ISSN: 1380-2933. Pub. country: Netherlands. Language: English.

AB BACKGROUND: Antibody-based reagents have failed to live up to their anticipated role as highly specific targeting agents for cancer therapy. Targeting with human single-chain Fv (sFv) molecules may overcome some of the limitations of murine IgG, but are difficult to produce with conventional hybridoma technology. Alternatively, phage display of antibody gene repertoires can be used to produce human sFv. OBJECTIVES: To isolate and characterize human single chain Fvs which bind to c-erbB-2, an oncogene product overexpressed by 30-50% of breast carcinomas and other adenocarcinomas. STUDY DESIGN: A non-immune human single-chain Fv phage antibody library was selected on human c-erbB extracellular domain and sFv characterized with respect to affinity, binding kinetics, and in vivo pharmacokinetics in tumor-bearing scid mice. RESULTS: A human

single-chain Fv (C6.5) was isolated which binds specifically to c-erbB-2. C6.5 is entirely human in sequence, expresses at high level as native protein in E. coli, and is easily purified in high yield in two steps. C6.5 binds to immobilized c-erbB-2 extracellular domain with a Kd of 1.6 x 10(-8) M and to c-erbB-2 on SK-OV-3 cells with a Kd of 2.0 x 10(-8) M, an affinity that is similar to sFv produced against the same antigen from hybridomas. Biodistribution studies demonstrate 1.47% injected dose/g tumor 24 h after injection of 125I-C6.5 into scid mice bearing SK-OV-3 tumors. Tumor:normal organ ratios range from 8.9:1 for kidney to 283:1 for muscle. CONCLUSIONS: These results are the first in vivo biodistribution studies using an sFv isolated from a non-immune human repertoire and confirm the specificity of sFv produced in this manner. The use of phage display to produce C6.5 mutants with higher affinity and slower k(off) would permit rigorous evaluation of the role of antibody affinity and binding kinetics in tumor targeting, and could result in the production of a therapeutically useful targeting protein for radioimmunotherapy and other applications.

L11 ANSWER 6 OF 35 MEDLINE on STN

1998040638. PubMed ID: 9373307. An overview of the 1996 Keystone meeting. Exploring and exploiting antibody and Ig superfamily combining sites. **Huston J S**; Haber E. (Creative BioMolecules, Hopkinton, MA 01748, USA.. huston@bbri.harvard.edu) . Immunotechnology : an international journal of immunological engineering, (1996 Nov) Vol. 2, No. 4, pp. 253-60. Journal code: 9511979. ISSN: 1380-2933. Pub. country: Netherlands. Language: English.

L11 ANSWER 7 OF 35 MEDLINE on STN

97121141. PubMed ID: 8961808. Single-chain Fv radioimmunotargeting. **Huston J S**; George A J; Adams G P; Stafford W F; Jamar F; Tai M S; McCartney J E; Oppermann H; Heelan B T; Peters A M; Houston L L; Bookman M A; Wolf E J; Weiner L M. (Creative BioMolecules, Inc., Department of Immunology, Royal Postgraduate Medical School, Hammersmith Hospital, London, United Kingdom.) The quarterly journal of nuclear medicine : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), (1996 Sep) Vol. 40, No. 3, pp. 320-33. Ref: 61. Journal code: 9512274. ISSN: 1125-0135. Pub. country: Italy. Language: English.

AB The availability of engineered antibody species has catalyzed new developments in radioimmunotargeting. This chapter summarized recent studies of single-chain Fv (sFv) proteins, which are minimal antibody binding sites engineered as single polypeptide chains. The single-chain Fv can be as small as 26 kDa monomers or may be engineered as larger fusion proteins designed to self-associate into dimeric or multimeric species. They typically exhibit rapid clearance that results in high targeting specificity within a matter of hours. We have compared different modes of administration to allow further manipulation of their biodistribution and targeting properties. Results of the present study comparing intravenous (i.v.) and intraperitoneal (i.p.) administration show comparable long-term retention in circulation, but the i.v. route showed an initially high peak blood level while i.p. injection did not. As with a single sFv dose, repeated bolus injections of sFv attained high target-to-background ratios, whereas continuous sFv infusion reached a steady state level of free sFv in blood and kidney that exceeded that in tumor xenografts. We observed improved localization of radioiodinated sFv in tumor xenografts if the radioiodine label resisted dehalogenation from the protein, which was accomplished, for example, through conjugation of a para-131I-benzoyl group to Iysyl epsilon-amino groups of the protein. Modification of the sFv by genetic incorporation of a cysteinyl peptide (to form sFv') provided a chelation site for radiometals that simplified incorporation of 99mTc with the opportunity for improved diagnostic imaging in cancer and other diseases. Therapeutic applications of sFv

radioimmunotargeting could rely on sFv' complexed to 186Re or 188Re. Engineering sFv of sFv' with increased antigen-binding affinity and appropriately manipulating their mode of administration should promote sustained tumor retention conducive to clinically useful therapeutic indices.

L11 ANSWER 8 OF 35 MEDLINE on STN
97064752. PubMed ID: 8908302. Antibody binding sites. **Huston J S**; Margolies M N; Haber E. (Creative BioMolecules, Inc., Hopkinton, Massachusetts 01748, USA.) Advances in protein chemistry, (1996) Vol. 49, pp. 329-450. Ref: 326. Journal code: 0116732. ISSN: 0065-3233. Pub. country: United States. Language: English.

L11 ANSWER 9 OF 35 MEDLINE on STN
97044103. PubMed ID: 8889174. Symmetry of Fv architecture is conducive to grafting a second antibody binding site in the Fv region. Keck P C; **Huston J S**. (Creative BioMolecules, Hopkinton, Massachusetts 01748, USA.) Biophysical journal, (1996 Oct) Vol. 71, No. 4, pp. 2002-11. Journal code: 0370626. ISSN: 0006-3495. Pub. country: United States. Language: English.
AB Molecular modeling studies on antibody Fv regions have been pursued to design a second antigen-binding site (chi-site) in a chimeric single-chain Fv (chi sFv) species of about 30 kDa. This analysis has uncovered an architectural basis common to many Fv regions that permits grafting a chi-site onto the Fv surface that diametrically opposes the normal combining site. By using molecular graphics analysis, chimeric complementarity-determining regions (chi CDRs) were defined that comprised most of the CDRs from an antibody binding site of interest. The chain directionality of chi CDRs was consistent with that of specific bottom loops of the sFv, which allowed for grafting of chi CDRs with an overall geometry approximating CDRs in the parent combining site. Analysis of 10 different Fv crystal structures indicates that the positions for inserting chi CDRs are very highly conserved, as are the corresponding chi CDR boundaries in the parent binding site. The results of this investigation suggest that it should be possible to generally apply this approach to the development of chimeric bispecific antibody binding site (chi BABS) proteins.

L11 ANSWER 10 OF 35 MEDLINE on STN
96101662. PubMed ID: 8523119. Enhanced tumor specificity of 741F8-1 (sFv')2, an anti-c-erbB-2 single-chain Fv dimer, mediated by stable radioiodine conjugation. Adams G P; McCartney J E; Wolf E J; Eisenberg J; **Huston J S**; Bookman M A; Moldofsky P; Stafford W F 3rd; Houston L L; Weiner L M. (Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania.) Journal of nuclear medicine : official publication, Society of Nuclear Medicine, (1995 Dec) Vol. 36, No. 12, pp. 2276-81. Journal code: 0217410. ISSN: 0161-5505. Pub. country: United States. Language: English.
AB The goal of this study was to determine if the stabilization of the radioiodine-protein bond by the N-succinimidyl p-iodobenzoate (PIB) method improved the degree and specificity of tumor localization of 125I-741F8-1 (sFv')2, an anti-c-erbB-2 sFv dimer, in an immunodeficient murine model. METHODS: Gamma camera images were acquired 21 hr after intravenous administration of 131I-741F8-1 (sFv')2 labeled by the p-iodobenzoate or chloramine T methods. The stability of the radioiodine-protein bond also was assessed in plasma samples after intravenous injection of 125I-741F8-1 (sFv')2 labeled by either the chloramine T or p-iodobenzoate methods. RESULTS: By 6 hr postinjection, 97% of the activity associated with the 125I-741F8-1 (sFv')2 labeled by the p-iodobenzoate method was protein bound compared with 61% after labeling with the chloramine-T method. These observations indicate that increasing the stability of the conjugation between the radioiodine and the sFv molecule can significantly

increase the degree and specificity of tumor targeting. Significantly greater tumor retention ($p < 0.005$) and lower blood ($p < 0.001$), spleen ($p < 0.001$) and stomach ($p < 0.005$) retention were observed in biodistribution studies when the p-iodobenzoate conjugate was used. This resulted in superior tumor-to-organ ratios for all tissue samples studied. CONCLUSION: These observations may have clinical relevance for the use of radiolabeled sFv as imaging agents.

L11 ANSWER 11 OF 35 MEDLINE on STN
96092923. PubMed ID: 8521448. Redirection of cellular cytotoxicity. A two-step approach using recombinant single-chain Fv molecules. George A J; Titus J A; Jost C R; Kurucz I; Perez P; Andrew S M; Nicholls P J; **Huston J S**; Segal D M. (Department of Immunology, Royal Postgraduate Medical School, Hammersmith Hospital, London, UK.) Cell biophysics, (1995 Jun) Vol. 26, No. 3, pp. 153-65. Ref: 39. Journal code: 8002185. ISSN: 0163-4992. Pub. country: United States. Language: English.
AB In this article the authors discuss an indirect system for redirecting cellular cytotoxicity, which utilizes a "universal" bispecific antibody to redirect T-cells to kill cells targeted with single-chain Fv (sFv) fusion proteins that carry a peptide tag recognized by the bispecific antibody. This approach has a number of theoretical advantages in the immunotherapy of cancer.

L11 ANSWER 12 OF 35 MEDLINE on STN
95323948. PubMed ID: 7600561. Optimization of in vivo tumor targeting in SCID mice with divalent forms of 741F8 anti-c-erbB-2 single-chain Fv: effects of dose escalation and repeated i.v. administration. Adams G P; McCartney J E; Wolf E J; Eisenberg J; Tai M S; **Huston J S**; Stafford W F 3rd; Bookman M A; Houston L L; Weiner L M. (Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA.) Cancer immunology, immunotherapy : CII, (1995 May) Vol. 40, No. 5, pp. 299-306. Journal code: 8605732. ISSN: 0340-7004. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB Single-chain Fv molecules in monovalent (sFv) and divalent [(sFv')2] forms exhibit highly specific tumor targeting in mice as a result of their small size and rapid systemic clearance. As a consequence, there is a rapid reversal of the sFv blood/tumor gradient, resulting in diminished retention of sFv species in tumors. In this report we investigate two distinct strategies, dose escalation and repetitive intravenous (i.v.) dosing, aiming to increase the absolute selective retention of radiolabeled anti-c-erbB-2 125I-741F8 (sFv')2 in c-erbB-2-overexpressing SK-OV-3 tumors in mice with severe combined immunodeficiency (SCID). A dose-escalation strategy was applied to single i.v. injections of 125I-741F8 (sFv')2. Doses from 50 micrograms to 1000 micrograms were administered without a significant decrease in tumor targeting or specificity. High doses resulted in large increases in the absolute retention of 125I-741F8 (sFv')2. For example, raising the administered dose from 50 micrograms to 1000 micrograms increased the tumor retention 24 h after injection from 0.46 microgram/g to 9.5 micrograms/g, and resulted in a net increase of greater than 9 micrograms/g. Over the same dose range, the liver retention rose from 0.06 microgram/g to 1 microgram/g, and resulted in a net increase of less than 1 microgram/g. The retention of 9.5 micrograms/g in tumor 24 h following the 1000-micrograms dose of (sFv')2 was comparable to that seen 24 h after a 50-micrograms dose of 125I-741F8 IgG, indicating that the use of large doses of (sFv')2 may partially offset their rapid clearance. When two doses were administered by i.v. injection 24 h apart, the specificity of delivery to tumor observed after the first dose was maintained following the second injection. Tumor retention of 125I-741F8 (sFv')2 was 0.32 microgram/g at 24 h and 0.22 micrograms/g at 48 h following a single injection of 20 micrograms, while 0.04 microgram/ml and 0.03 microgram/ml were retained in blood at the same assay times. After a second

20-micrograms injection at the 24-h assay time, tumor retention increased to 0.49 micrograms/g, and blood retention was 0.06 microgram/ml, at the 48-h point. These results suggest that multiple high-dose administrations of radiolabeled 741F8 (sFv')2 may lead to the selective tumor localization of therapeutic radiation doses.

L11 ANSWER 13 OF 35 MEDLINE on STN

95254582. PubMed ID: 7736532. Tumor targeting in a murine tumor xenograft model with the (sFv')2 divalent form of anti-c-erbB-2 single-chain Fv. **Huston J S**; Adams G P; McCartney J E; Tai M S; Hudziak R M; Oppermann H; Stafford W F 3rd; Liu S; Fand I; Apell G; +. (Creative BioMolecules, Inc., Hopkinton, MA 01748.) Cell biophysics, (1994) Vol. 24-25, pp. 267-78. Journal code: 8002185. ISSN: 0163-4992. Pub. country: United States. Language: English.

AB This investigation has utilized novel forms of the single-chain Fv (sFv), wherein a cysteine-containing peptide has been fused to the sFv carboxyl terminus to facilitate disulfide bonding or specific cross-linking of this sFv' to make divalent (sFv')2. The 741F8 anti-c-erbB-2 monoclonal antibody was used as the basis for construction of 741F8 sFv, from which the sFv' and (sFv')2 derivatives were prepared. Recombinant c-erbB-2 extracellular domain (ECD) was prepared in CHO cells and the bivalency of 741F8 (sFv')2 demonstrated by its complex formation with ECD. The tumor binding properties of 125I-labeled anti-c-erbB-2 741F8 sFv, sFv', and (sFv)2 were compared with radiolabeled antidigoxin 26-10 sFv' and (sFv')2 controls. Following intravenous administration of radiolabeled species to severe combined immune-deficient (SCID) mice bearing SK-OV-3 tumors (which over-express c-erbB-2), blood and organ samples were obtained as a function of time over 24 h. Comparative analysis of biodistribution and tumor-to-organ ratios demonstrated the 741F8 sFv, sFv', and (sFv')2 had excellent specificity for tumors, which improved with time after injection. This contrasted with nonspecific interstitial pooling in tumors observed with the 26-10 sFv, sFv', and (sFv')2, which decreased with time after administration. Tumor localization was significantly better for disulfide or peptide crosslinked 741F8 (sFv')2 having Gly4Cys tails than for monovalent 741F8 sFv' or Fab. The superior properties of the 741F8 (sFv')2 in targeting SK-OV-3 tumors in SCID mice suggests the importance of further investigations of divalent sFv analogs for immunotargeting.

L11 ANSWER 14 OF 35 MEDLINE on STN

95196234. PubMed ID: 7889539. Antigen recognition and targeted delivery by the single-chain Fv. **Huston J S**; Tai M S; McCartney J; Keck P; Oppermann H. (Creative BioMolecules, Inc., Hopkinton, MA 01748.) Cell biophysics, (1993 Jan-Jun) Vol. 22, No. 1-3, pp. 189-224. Ref: 108. Journal code: 8002185. ISSN: 0163-4992. Pub. country: United States. Language: English.

AB The single-chain Fv (sFv) has proven attractive for immuno-targeting, both alone and as a targeting element within sFv fusion proteins. This chapter summarizes the features of sFv proteins that have sparked this interest, starting with the conservation of Fv architecture that makes general sFv design practical. The length and composition of linkers used to bridge V domains are discussed based on the sFv literature; special emphasis is given to the (Gly4Ser)3 15-residue linker that has proven of broad utility for constructing Fv regions of antibodies and other members of the immunoglobulin superfamily. The refolding properties of sFv proteins are summarized and examples given from our laboratory. Spontaneous refolding from the fully reduced and denatured state, typified by 26-10 sFv, is contrasted with disulfide-restricted refolding, exemplified by MOPC 315 and R11D10 sFv proteins, which recover antigen binding only if their disulfides have been oxidized prior to removal of denaturant. The medical value of sFv proteins hinges on their reliability in antigen recognition and rapidity in targeted delivery. Detailed analysis of specificity and affinity of antigen binding by the 26-10 antidigoxin sFv has demonstrated

very high fidelity to the binding properties of the parent 26-10 sFv. These results gave confidence to the pursuit of more complex biomedical applications of these proteins, which is indicated by our work with the R11D10 sFv for the imaging of myocardial infarctions. Diagnostic imaging and therapeutic immunotargeting by sFv present significant opportunities, particularly as a result of their pharmacokinetic properties. Intravenously administered sFv offers much faster clearance than conventional Fab fragments or intact immunoglobulin with minimal background binding.

L11 ANSWER 15 OF 35 MEDLINE on STN

94361794. PubMed ID: 7765352. Mammalian cell expression of single-chain Fv (sFv) antibody proteins and their C-terminal fusions with interleukin-2 and other effector domains. Dorai H; McCartney J E; Hudziak R M; Tai M S; Laminet A A; Houston L L; **Huston J S**; Oppermann H. (Creative BioMolecules, Inc., Hopkinton, MA 01748.) Bio/technology (Nature Publishing Company), (1994 Sep) Vol. 12, No. 9, pp. 890-7. Journal code: 8309273. ISSN: 0733-222X. Pub. country: United States. Language: English.

AB The production of several single-chain Fv (sFv) antibody proteins was examined by three modes of mammalian cell expression. Our primary model was the 741F8 anti-c-erbB-2 sFv, assembled as either the VH-VL or VL-VH, and expressed alone, with C-terminal cysteine for dimerization, or as fusion proteins with carboxyl-terminal effector domains, including interleukin-2, the B domain of staphylococcal protein A, the S-peptide of ribonuclease S, or hexa-histidine metal chelate peptide. Constructs were expressed and secreted transiently in 293 cells and stably in CHO or Sp2/0 cell lines, the latter yielding up to 10 mg per liter. Single-chain constructs of MOPC 315 myeloma and 26-10 monoclonal antibodies were also expressed, as were hybrids comprising unrelated VH and VL regions. Our results suggest that mammalian expression is a practical and valuable complement to the bacterial expression of single-chain antibodies.

L11 ANSWER 16 OF 35 MEDLINE on STN

94165475. PubMed ID: 8120389. Redirection of T cell-mediated cytotoxicity by a recombinant single-chain Fv molecule. George A J; Titus J A; Jost C R; Kurucz I; Perez P; Andrew S M; Nicholls P J; **Huston J S**; Segal D M. (Experimental Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.) Journal of immunology (Baltimore, Md. : 1950), (1994 Feb 15) Vol. 152, No. 4, pp. 1802-11. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB We have produced two single-chain Fv (sFv) proteins by bacterial periplasmic secretion, one sFv with specificity for the hapten DNP, and the other for the human transferrin receptor. After solubilization and refolding, we recovered several mg of active sFv per liter of bacterial culture. Each sFv bound to cells bearing the appropriate Ag and could be used to direct targeted cellular cytotoxicity. Targeting relied on a universal bispecific antibody designed to cross-link CD3 on the cytotoxic T cell with a peptide fused to the sFv carboxyl-terminus. The universal bispecific antibody was used in combination with the Ag-specific sFv to redirect human cytotoxic T cells to kill a variety of target cells. Such an approach has a number of advantages that may make it useful for the immunotherapy of cancer and other diseases.

L11 ANSWER 17 OF 35 MEDLINE on STN

93367344. PubMed ID: 8360586. Medical applications of single-chain antibodies. **Huston J S**; McCartney J; Tai M S; Mottola-Hartshorn C; Jin D; Warren F; Keck P; Oppermann H. (Creative BioMolecules, Inc., Hopkinton, MA 01748.) International reviews of immunology, (1993) Vol. 10, No. 2-3, pp. 195-217. Ref: 113. Journal code: 8712260. ISSN: 0883-0185. Pub. country: Switzerland. Language: English.

AB A single-chain antibody or single-chain Fv (sFv) incorporates the complete

antibody binding site in a single polypeptide chain of minimal size, with an approximate molecular weight of 26,000. In antibodies, the antigen combining site is part of the Fv region, which is composed of the VH and VL variable domains on separate heavy and light chains. Efforts over nearly two decades have indicated that Fv fragments can only rarely be prepared from IgG and IgA antibodies by proteolytic dissection. Beginning in 1988, single-chain analogues of Fv fragments and their fusion proteins have been reliably generated by antibody engineering methods. The first step involves obtaining the genes encoding VH and VL domains with desired binding properties; these V genes may be isolated from a specific hybridoma cell line, selected from a combinatorial V-gene library, or made by V gene synthesis. The single-chain Fv is formed by connecting the component V genes with an oligonucleotide that encodes an appropriately designed linker peptide, such as (Gly4-Ser)3. The linker bridges the C-terminus of the first V region and N-terminus of the second, ordered as either VH-linker-VL or VL-linker-VH. In principle, the sFv binding site can faithfully replicate both the affinity and specificity of its parent antibody combining site, as demonstrated in our model studies with the 26-10 anti-digoxin sFv. Furthermore, the sFv remains stable at low concentrations that promote VH and VL dissociation from the Fv heterodimer, resulting in loss of Fv binding. Intravenously administered sFv proteins exhibit accelerated biodistribution and exceptionally fast clearance compared to IgG or Fab. These pharmacokinetic properties allow rapid imaging by sFv, which therefore may be labeled with a short-lived isotope such as Tc-99m. Expression of a single gene product from fused sFv and effector genes facilitates immunotargeting of the effector protein, as shown for single-chain Fv toxin fusion proteins.

L11 ANSWER 18 OF 35 MEDLINE on STN

93364902. PubMed ID: 7689421. Highly specific in vivo tumor targeting by monovalent and divalent forms of 741F8 anti-c-erbB-2 single-chain Fv. Adams G P; McCartney J E; Tai M S; Oppermann H; **Huston J S**; Stafford W F 3rd; Bookman M A; Fand I; Houston L L; Weiner L M. (Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111.) Cancer research, (1993 Sep 1) Vol. 53, No. 17, pp. 4026-34. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB The in vivo properties of monovalent and divalent single-chain Fv (sFv)-based molecules with the specificity of the anti-c-erbB-2 monoclonal antibody 741F8 were examined in scid mice bearing SK-OV-3 tumor xenografts. 741F8 sFv monomers exhibited rapid, biphasic clearance from blood, while a slightly slower clearance was observed with the divalent 741F8 (sFv')2 comprising a pair of 741F8 sFv' with a C-terminal Gly4Cys joined by a disulfide bond. Following i.v. injection, the 741F8 sFv monomer was selectively retained in c-erbB-2-overexpressing SK-OV-3 tumor, with excellent tumor:normal organ ratios uniformly exceeding 10:1 by 24 h. The specificity of this effect was demonstrated by the lack of retention of the anti-digoxin 26-10 sFv monomer, as evaluated by biodistribution studies, gamma camera imaging, and cryomacroautoradiography studies. The specificity index (741F8 sFv retention/26-10 sFv retention) of 741F8 monomer binding, measured by the percentage of injected dose per g of tissue, was 13.2:1 for tumor, and 0.8 to 2.1 for all tested normal organs, with specificity indices for tumor:organ ratios ranging from 7.0 (kidneys) to 16.7 (intestines). Comparing divalent 741F8 (sFv')2 with the 26-10 (sFv')2, similar patterns emerged, with specificity indices for retention in tumor of 16.9 for the Gly4Cys-linked (sFv')2. These data demonstrate that, following their i.v. administration, both monovalent and divalent forms of 741F8 sFv are specifically retained by SK-OV-3 tumors. This antigen-specific binding, in conjunction with the 26-10 sFv controls, precludes the possibility that passive diffusion and pooling in the tumor interstitium contributes significantly to long-term tumor localization. 741F8 (sFv')2 species with peptide spacers exhibited divalent binding and increased retention in tumors as compared with 741F8 sFv monomers. Since

the blood retention of the (sFv')2 is slightly more prolonged than that of the monomer, it was necessary to demonstrate that the increased tumor localization of the peptide-linked (sFv')2 was due to its divalent nature. The significantly greater localization of the divalent bismalimidohexane-linked 741F8 (sFv')2 as compared with a monovalent 741F8 Fab fragment of approximately the same size suggests that the increased avidity of the (sFv')2 is a factor in its improved tumor retention. This is the first report of successful specific in vivo targeting of tumors by divalent forms of sFv molecules. The improved retention of specific divalent (sFv')2 by tumors may have important consequences for targeted diagnostic or therapeutic strategies.

L11 ANSWER 19 OF 35 MEDLINE on STN

93267717. PubMed ID: 8497018. The effect of high- and low-intensity warm-up on the physiological responses to a standardized swim and tethered swimming performance. Mitchell J B; **Huston J S**. (Department of Physical Education, Texas Christian University, Fort Worth 76129.) Journal of sports sciences, (1993 Apr) Vol. 11, No. 2, pp. 159-65. Journal code: 8405364. ISSN: 0264-0414. Pub. country: ENGLAND: United Kingdom. Language: English.

AB This investigation was conducted to determine the effect of high- and low-intensity warm-ups on physiological responses, lactate accumulation, and high-intensity freestyle and tethered swimming performance. Ten male collegiate swimmers were tested for maximal oxygen uptake (VO2 max) followed by two series of three warm-up protocols performed in a randomized order at least 2 days apart. The warm-up protocols were: (1) no warm-up (NWU), (2) a 366-m swim at 70% VO2 max (LWU) and (3) four 46-m swims at 1-min intervals at a speed corresponding to 110% VO2 max (HWU). Five minutes after each warm-up in the first series, the swimmers swam a 183-m standardized freestyle swim at a velocity corresponding to 110% VO2 max, and 5 min after each warm-up in the second series the swimmers completed a tethered swim to exhaustion with a weight attached to the tether to elicit fatigue at about 2 min. Three minutes after each warm-up and 3 min after each standardized and tethered swim, a finger-prick blood sample for lactate measurement was obtained. Heart rate and VO2 were also measured during the warm-up and the standardized and tethered swims. The performance times in the tethered swim were not significantly different between the three conditions (116.8 +/- 46.8, 137 +/- 53.3 and 122.94 +/- 37.2 s for the NWU, LWU and HWU, respectively).(ABSTRACT TRUNCATED AT 250 WORDS)

L11 ANSWER 20 OF 35 MEDLINE on STN

92288242. PubMed ID: 1600106. Multisite association by recombinant proteins can enhance binding selectivity. Preferential removal of immune complexes from serum by immobilized truncated FB analogues of the B domain from staphylococcal protein A. **Huston J S**; Cohen C; Maratea D; Fields F; Tai M S; Cabral-Denison N; Juffras R; Rueger D C; Ridge R J; Oppermann H; +. (Creative Biomolecules, Incorporated, Hopkinton, Massachusetts 01748.) Biophysical journal, (1992 Apr) Vol. 62, No. 1, pp. 87-91. Journal code: 0370626. ISSN: 0006-3495. Pub. country: United States. Language: English.

L11 ANSWER 21 OF 35 MEDLINE on STN

92272920. PubMed ID: 1815591. Biosynthetic antibody binding sites: development of a single-chain Fv model based on antidinitrophenol IgA myeloma MOPC 315. McCartney J E; Lederman L; Drier E A; Cabral-Denison N A; Wu G M; Batorsky R S; **Huston J S**; Oppermann H. (Creative BioMolecules, Inc., Hopkinton, Massachusetts 01748.) Journal of protein chemistry, (1991 Dec) Vol. 10, No. 6, pp. 669-83. Ref: 52. Journal code: 8217321. ISSN: 0277-8033. Pub. country: United States. Language: English.

AB The functional antigen binding region of antidinitrophenol mouse IgA myeloma MOPC 315 has been produced as a single-chain Fv (sFv) protein in E. coli. Recombinant 315 proteins included sFv alone, a bifunctional

fusion protein with amino-terminal fragment B (FB) of staphylococcal protein A, and a two-chain 315 Fv fragment. Successful refolding of the 315 sFv required formation of disulfide bonds while the polypeptide was in a denatured state, as previously observed for the parent Fv fragment. Affinity-purified recombinant 315 proteins showed full recovery of specific activity, with values for Ka,app of 1.5 to 2.2 x 10(6) M-1, equivalent to the parent 315 Fv fragment. As observed for natural 315 Fv, the sFv region of active FB-sFv315 fusion protein was resistant to pepsin treatment, whereas inactive protein was readily degraded. These experiments will allow the application of protein engineering to the 315 single-chain Fv; such studies can advance structure-function studies of antibody combining sites and lead to an improved understanding of single-chain Fv proteins.

L11 ANSWER 22 OF 35 MEDLINE on STN

92107082. PubMed ID: 1762568. Protein engineering of single-chain Fv analogs and fusion proteins. **Huston J S**; Mudgett-Hunter M; Tai M S; McCartney J; Warren F; Haber E; Oppermann H. Methods in enzymology, (1991) Vol. 203, pp. 46-88. Journal code: 0212271. ISSN: 0076-6879. Pub. country: United States. Language: English.

L11 ANSWER 23 OF 35 MEDLINE on STN

91084470. PubMed ID: 2261460. A bifunctional fusion protein containing Fc-binding fragment B of staphylococcal protein A amino terminal to antidigoxin single-chain Fv. Tai M S; Mudgett-Hunter M; Levinson D; Wu G M; Haber E; Oppermann H; **Huston J S**. (Creative BioMolecules, Inc., Hopkinton, Massachusetts 01748.) Biochemistry, (1990 Sep 4) Vol. 29, No. 35, pp. 8024-30. Journal code: 0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.

AB A bifunctional molecule was genetically engineered which contained an amino-terminal effector domain that bound immunoglobulin Fc (fragment B of staphylococcal protein A) and a carboxyl-terminal domain that bound digoxin [a single-chain Fv (sFv)]. Effector and sFv binding properties were virtually identical with those of the parent molecules, despite the proximity of the FB to the sFv combining site. This finding is unprecedented since in all molecules of the natural immunoglobulin superfamily, the antigen binding domain is amino terminal to the effector domain. The FB-sFv sequence was encoded in a single synthetic gene and expressed as a 33,106 molecular weight protein in Escherichia coli. After purification, renaturation, and affinity isolation, yield of active fusion protein were 110 mg/L of fermented cells (18.5-g cell paste). Bifunctionality was confirmed by the ability of FB-sFv to cross-link IgG to digoxin-bovine serum albumin, as measured by plate assays and by Ouchterlony analysis. Analysis of the expressed fusion protein suggests that the sFv holds promise for the development of multifunctional, targetable single-chain proteins.

L11 ANSWER 24 OF 35 MEDLINE on STN

88320347. PubMed ID: 3045807. Protein engineering of antibody binding sites: recovery of specific activity in an anti-digoxin single-chain Fv analogue produced in Escherichia coli. **Huston J S**; Levinson D; Mudgett-Hunter M; Tai M S; Novotny J; Margolies M N; Ridge R J; Bruccoleri R E; Haber E; Crea R; +. (Creative Biomolecules, Hopkinton, MA 01748.) Proceedings of the National Academy of Sciences of the United States of America, (1988 Aug) Vol. 85, No. 16, pp. 5879-83. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB A biosynthetic antibody binding site, which incorporated the variable domains of anti-digoxin monoclonal antibody 26-10 in a single polypeptide chain (Mr = 26,354), was produced in Escherichia coli by protein engineering. This variable region fragment (Fv) analogue comprised the 26-10 heavy- and light-chain variable regions (VH and VL) connected by a 15-amino acid linker to form a single-chain Fv (sFv). The sFv was

designed as a prolyl-VH-(linker)-VL sequence of 248 amino acids. A 744-base-pair DNA sequence corresponding to this sFv protein was derived by using an E. coli codon preference, and the sFv gene was assembled starting from synthetic oligonucleotides. The sFv polypeptide was expressed as a fusion protein in E. coli, using a leader derived from the trp LE sequence. The sFv protein was obtained by acid cleavage of the unique Asp-Pro peptide bond engineered at the junction of leader and sFv in the fusion protein [(leader)-Asp-Pro-VH-(linker)-VL]. After isolation and renaturation, folded sFv displayed specificity for digoxin and related cardiac glycosides similar to that of natural 26-10 Fab fragments. Binding between affinity-purified sFv and digoxin exhibited an association constant [Ka = (3.2 +/- 0.9) x 10(7) M-1] that was about a factor of 6 smaller than that found for 26-10 Fab fragments [Ka = (1.9 +/- 0.2) x 10(8) M-1] under the same buffer conditions, consisting of 0.01 M sodium acetate, pH 5.5/0.25 M urea.

L11 ANSWER 25 OF 35 MEDLINE on STN

88163650. PubMed ID: 3126813. Identification of a receptor binding region on the beta subunit of human follicle-stimulating hormone. Schneyer A L; Sluss P M; **Huston J S**; Ridge R J; Reichert L E Jr. (Department of Biochemistry, Albany Medical College, New York 12208.) Biochemistry, (1988 Jan 26) Vol. 27, No. 2, pp. 666-71. Journal code: 0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.

AB Mouse epidermal growth factor (mEGF) and the beta subunit of follicle-stimulating hormone (hFSH) (hFSH-beta) have been shown to inhibit binding of intact hFSH to its testes membrane receptor in vitro. Both hFSH-beta and mEGF contain the tetrapeptide sequence Thr-Arg-Asp-Leu (TRDL). Previous results demonstrated that synthetic TRDL inhibited binding of intact hFSH to receptor. We therefore investigated the possibility that TRDL was located on an exposed region of FSH-beta using a polyclonal antiserum to hFSH [NHPP anti-hFSH batch 4 (AB4)] which recognized determinants on intact hFSH and its beta subunit, but not the alpha subunit. Pituitary FSH preparations from several mammalian species produced parallel inhibition curves in a heterologous [AB4 and 125I-labeled ovine FSH (125I-oFSH)] radioimmunoassay with relative potencies similar to those observed for the same preparations assayed by radioligand receptor assay. This antiserum also competitively inhibited 125I-FSH binding to receptor. Thus, AB4 appeared to recognize antigenic determinants that are highly conserved and located at or near regions involved with hormone recognition of receptor for FSH. Synthetic TRDL inhibited 50% of 125I-hFSH binding to antiserum at a concentration of 1.36 mg/tube (9 x 10(-3) M). Other tetrapeptides (Thr-Pro-Arg-Lys and Lys-Thr-Cys-Thr) had no inhibitory activity at comparable concentrations. A mixture of the free amino acids T, R, D, and L inhibited radioligand binding only at significantly higher concentrations than TRDL. (ABSTRACT TRUNCATED AT 250 WORDS)

L11 ANSWER 26 OF 35 MEDLINE on STN

86243394. PubMed ID: 3013310. Inhibition of iodine-125-labeled human follitropin binding to testicular receptor by epidermal growth factor and synthetic peptides. Sluss P M; Krystek S R Jr; Andersen T T; Melson B E; **Huston J S**; Ridge R; Reichert L E Jr. Biochemistry, (1986 May 6) Vol. 25, No. 9, pp. 2644-9. Journal code: 0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.

AB Two tetrapeptide sequence homologies between mouse epidermal growth factor precursor (mEGFP) and human follitropin (FSH) were revealed by a computer program that identifies identical residues among polypeptide sequences. The two tetrapeptides, Lys-Thr-Cys-Thr (KTCT) and Thr-Arg-Asp-Leu (TRDL), are present in the hormone-specific beta subunit of FSH from all species studied. These tetrapeptides are not present in the alpha subunit, which is common to all pituitary glycoprotein hormones. Both tetrapeptides are also found in mEGFP, and one tetrapeptide, TRDL, is located within the

53-residue form of mEGF purified from mouse submaxillary glands. Computer-generated hydropathy profiles predicted that both tetrapeptides are located in hydrophilic portions of the FSH beta subunit and that TRDL is in a hydrophilic portion of commercially available mEGF. Therefore, the tetrapeptides might be accessible to receptor binding sites for FSH. We report that mEGF inhibits binding of 125I-labeled human FSH to receptors in testis by 50% (I50) at a concentration of 1.8 X 10(-5) M. No binding inhibition was observed by GnRH or arginine-vasopressin at 10(-4) M, neither of which contain the tetrapeptide sequences. FSH beta subunit, which contains both tetrapeptides, also inhibited binding (I50 = 9 X 10(-8) M) of 125I-labeled human FSH to testis receptor. Thus, it appears that FSH beta subunit and mEGF are capable of inhibiting binding of FSH to testicular FSH receptors, presumably through interactions that include the homologous tetrapeptides. This presumption was supported by the observation that the synthetic tetrapeptides (KTCT or TRDL) were also active in inhibiting binding of 125I-labeled human FSH to testis receptor.

L11 ANSWER 27 OF 35 MEDLINE on STN

84158393. PubMed ID: 6323139. Differential effects of monovalent and bivalent antisera on the interaction of follicle-stimulating hormone with its receptor. Dias J A; **Huston J S**; Reichert L E Jr. Endocrinology, (1984 Apr) Vol. 114, No. 4, pp. 1259-65. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB In this study, polyclonal antisera to human FSH (hFSH) and its alpha- and beta-subunits have been used as probes of the interaction between hFSH and the FSH receptor from bovine testis. Preincubation of [125I]iodo-hFSH with antisera to the subunits of hFSH induced an augmentation in binding of radioiodinated hFSH to membrane receptors. If the antisera were made monovalent by papain digestion, all binding augmentation previously seen with bivalent antisera was eliminated. Furthermore, whereas bivalent antiserum to intact hFSH had no effect on [125I]iodo-hFSH binding to receptor, papain-generated monovalent antisera to hFSH strongly inhibited [125I]iodo-hFSH binding. Formation of [125I]iodo-hFSH-receptor complex reduces the ability of bivalent antibodies to FSH or its subunits to interact with the complex, as determined by immunoprecipitation studies. Our studies suggest that each FSH subunit interacts with the membrane receptor. These results also caution that a comparison of bivalent and monovalent antisera is necessary to determine if a particular antibody effects binding of hormone to receptor.

L11 ANSWER 28 OF 35 MEDLINE on STN

81260613. PubMed ID: 6266804. Effect of the structure-stabilizing agent glycerol on detergent-solubilized follicle-stimulating hormone receptors from calf testis. Dias J A; **Huston J S**; Reichert L E Jr. Endocrinology, (1981 Sep) Vol. 109, No. 3, pp. 736-42. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

L11 ANSWER 29 OF 35 MEDLINE on STN

81231086. PubMed ID: 7247405. Properties of disulfide-linked tubulin purified on hydroxyapatite and its comparison with intact and dissociated microtubules using limited tryptic digestion. Love W; Millay D; **Huston J S**. Archives of biochemistry and biophysics, (1981 Apr 1) Vol. 207, No. 2, pp. 300-10. Journal code: 0372430. ISSN: 0003-9861. Pub. country: United States. Language: English.

L11 ANSWER 30 OF 35 MEDLINE on STN

80117873. PubMed ID: 43400. Formation of 100 A filaments from purified glial fibrillary acidic protein in vitro. Rueger D C; **Huston J S**; Dahl D; Bignami A. Journal of molecular biology, (1979 Nov 25) Vol. 135, No. 1, pp. 53-68. Journal code: 2985088R. ISSN: 0022-2836. Pub. country: United States. Language: English.

L11 ANSWER 31 OF 35 MEDLINE on STN
79068860. PubMed ID: 722168. Laboratory study of commonly used microvascular clips. Blaschke M J; Osgood C P; **Huston J S**. The Journal of the Maine Medical Association, (1978 Dec) Vol. 69, No. 12, pp. 339-41. Journal code: 7505619. ISSN: 0025-0694. Pub. country: United States. Language: English.

L11 ANSWER 32 OF 35 MEDLINE on STN
77222134. PubMed ID: 880315. Structural properties of the glial fibrillary acidic protein. Evidence for intermolecular disulfide bonds. **Huston J S**; Bignami A. Biochimica et biophysica acta, (1977 Jul 22) Vol. 493, No. 1, pp. 93-103. Journal code: 0217513. ISSN: 0006-3002. Pub. country: Netherlands. Language: English.
AB Glial fibrillary acidic protein was purified from 4 M urea extracts of bovine brain by DEAE Bio-Gel A chromatography, 30% ammonium sulfate precipitation and hydroxylapatite chromatography. Subunits of about 54 000 daltons are present in solution as polydisperse distributions of polymers largely constrained by the presence of interchain disulfide linkages. Circular dichroism measurements indicate a native conformation containing some alpha-helical structure. The relevance of these findings to the cytoskeletal function of intermediate (80-100 A) filaments is discussed.

L11 ANSWER 33 OF 35 MEDLINE on STN
75127421. PubMed ID: 4616686. Characterization of the lac repressor species produced by limited tryptic cleavage. **Huston J S**; Foo-Penn W F; Bechtel K C; Jardetzky O. Biochemical and biophysical research communications, (1974 Nov 27) Vol. 61, No. 2, pp. 441-8. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

L11 ANSWER 34 OF 35 MEDLINE on STN
73025065. PubMed ID: 4628028. Properties of the Fd fragment from rabbit immunoglobulin G. **Huston J S**; Bjork I; Tanford C. Biochemistry, (1972 Nov 7) Vol. 11, No. 23, pp. 4256-62. Journal code: 0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.

L11 ANSWER 35 OF 35 MEDLINE on STN
72189231. PubMed ID: 5063709. Studies on the subunit molecular weight of beef heart lactate dehydrogenase. **Huston J S**; Fish W W; Mann K G; Tanford C. Biochemistry, (1972 Apr 25) Vol. 11, No. 9, pp. 1609-12. Journal code: 0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.

=> d his

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FILE 'USPATFULL' ENTERED AT 20:15:17 ON 27 SEP 2006
E HUSTON JAMES S/IN
L1 26 S E3
L2 7 S L1 AND (FRAMEWORK REGION?/CLM)
E OPPERMANN H/AU
E E12
L3 101 S E3-E5
L4 84 S L3 NOT L1
L5 0 S L4 AND (FRAMEWORK REGION?/CLM)

FILE 'WPIDS' ENTERED AT 20:20:02 ON 27 SEP 2006
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L6 20 S E3
L7 9 S L6 AND (FRAMEWORK REGION?)

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L8          138 S E3
L9          126 S L8 NOT L6
L10           0 S L9 AND (FRAMEWORK REGION?)

     FILE 'MEDLINE' ENTERED AT 20:23:24 ON 27 SEP 2006
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L12           0 S L11 AND (FRAMEWORK REGION?)

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E4           50     OPPERMANN H C/AU
E5            5     OPPERMANN H J/AU
E6            1     OPPERMANN HANS C/AU
E7            2     OPPERMANN I/AU
E8           60     OPPERMANN J/AU
E9           13     OPPERMANN J A/AU
E10           1     OPPERMANN JANNAH D/AU
E11           1     OPPERMANN JOACHIM/AU
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=> s e3
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L14          65 L13 NOT L11

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L15           1 L14 AND (FRAMEWORK)

=> d l15,cbib,ab

L15  ANSWER 1 OF 1     MEDLINE on STN
2003009563.    PubMed ID: 12516018.   [Efforts concerning the health target of
     age-specific coverage levels in over 90% of the population of
     Saxony-Anhalt].   Von den Muhen der Ebene: Gesundheitsziel "Erreichen
     eines altersgerechten Impfstatus bei uber 90% der Bevolkerung" in
     Sachsen-Anhalt. Oppermann H; Kolbe M. (Landesuntersuchungsamt fur
     Gesundheits-, Umwelt- und Verbraucherschutz Sachsen-Anhalt, Fachbereich
     Gesundheit/Hygiene/Epidemiologie. ) Gesundheitswesen (Bundesverband der
     rzte des  ffentlichen Gesundheitsdienstes (Germany)), (2002 Dec) Vol. 64,
     No. 12, pp. 664-8.  Journal code: 9204210. ISSN: 0941-3790. Pub. country:
     Germany: Germany, Federal Republic of. Language: German.
AB   At the first health conference in Saxony-Anhalt held at Magdeburg in March
     1998 six health objectives were defined, among them the objective to
     increase to 90% the vaccination coverage level of the population.  To
     achieve this goal the participants decided to establish a working group
     composed of representatives of 20 institutions and organisations
     interested in vaccination strategies.  Subgroups were constituted for the
     following components of the objective: improvement of the data basis,
     completion of the special knowledge of physicians and other medical
     personnel, public information campaigns, and improvement of the structural
     framework.  More than 50 actions per year were initiated or co-ordinated
     taking into account the special profiles of the institutions and
     organisations involved.  In this way a better identification of the
     participants with the project was achieved and waste of strength and time
     was avoided.  The data basis was assessed using generally available or
     newly created parameters such as the incidence of notified
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vaccine-preventable diseases, measles seroprevalence, and vaccination coverage levels among children aged 5-6 years. Approaches to target group related activities of the working group were derived from these parameters. The most remarkable results of these activities include the definition of age specific vaccination coverage levels, the establishment of a certificate for physicians who have completed a vaccination training course, a monthly press release on vaccination subjects, the design of a poster presentation, the composition of foil-based age group specific lectures, and the establishment of frame conditions for a recall system for practising physicians. The first hurdles on the way to a high age specific vaccination coverage levels have been taken. Further work must be done to improve the use of offered vaccinations and to complete the available data. Therefore, additional target group-related projects and actions are planned for the years to come.

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=> d his

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                E OPPERMANN H/AU
                E E12
L3          101 S E3-E5
L4           84 S L3 NOT L1
L5            0 S L4 AND (FRAMEWORK REGION?/CLM)

     FILE 'WPIDS' ENTERED AT 20:20:02 ON 27 SEP 2006
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L6           20 S E3
L7            9 S L6 AND (FRAMEWORK REGION?)
                E OPPERMANN H/IN
L8          138 S E3
L9          126 S L8 NOT L6
L10           0 S L9 AND (FRAMEWORK REGION?)

     FILE 'MEDLINE' ENTERED AT 20:23:24 ON 27 SEP 2006
                E HUSTON J S/AU
L11          35 S E3
L12           0 S L11 AND (FRAMEWORK REGION?)
                E OPPERMANN H/AU
L13          75 S E3
L14          65 S L13 NOT L11
L15           1 S L14 AND (FRAMEWORK)

=> file uspatful
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    13.17      99.45

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FILE LAST UPDATED: 26 Sep 2006 (20060926/ED)
HIGHEST GRANTED PATENT NUMBER: US7114185
HIGHEST APPLICATION PUBLICATION NUMBER: US2006212984
CA INDEXING IS CURRENT THROUGH 26 Sep 2006 (20060926/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 26 Sep 2006 (20060926/PD)
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REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006


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=> sl16 and (complementarity determining region?/clm)
SL16 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

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          1299 COMPLEMENTARITY/CLM
        425096 DETERMINING/CLM
        367861 REGION?/CLM
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L17        197 L16 AND (COMPLEMENTARITY DETERMINING REGION?/CLM)

=> s l17 and linker/clm
          8258 LINKER/CLM
L18         17 L17 AND LINKER/CLM

=> d his

     (FILE 'HOME' ENTERED AT 20:15:09 ON 27 SEP 2006)

     FILE 'USPATFULL' ENTERED AT 20:15:17 ON 27 SEP 2006
                E HUSTON JAMES S/IN
L1           26 S E3
L2            7 S L1 AND (FRAMEWORK REGION?/CLM)
                E OPPERMANN H/AU
                E E12
L3          101 S E3-E5
L4           84 S L3 NOT L1
L5            0 S L4 AND (FRAMEWORK REGION?/CLM)

     FILE 'WPIDS' ENTERED AT 20:20:02 ON 27 SEP 2006
                E HUSTON J S/IN
L6           20 S E3
L7            9 S L6 AND (FRAMEWORK REGION?)
                E OPPERMANN H/IN
L8          138 S E3
L9          126 S L8 NOT L6
L10           0 S L9 AND (FRAMEWORK REGION?)

     FILE 'MEDLINE' ENTERED AT 20:23:24 ON 27 SEP 2006
                E HUSTON J S/AU
L11          35 S E3
L12           0 S L11 AND (FRAMEWORK REGION?)
                E OPPERMANN H/AU
L13          75 S E3
L14          65 S L13 NOT L11
L15           1 S L14 AND (FRAMEWORK)

     FILE 'USPATFULL' ENTERED AT 20:32:29 ON 27 SEP 2006
L16         380 S (FRAMEWORK REGION?/CLM)
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L17         197 S L16 AND (COMPLEMENTARITY DETERMINING REGION?/CLM)
L18          17 S L17 AND LINKER/CLM

=> s l18 not l1
L19         11 L18 NOT L1

=> d l19,cbib,clm,1-11

L19  ANSWER 1 OF 11  USPATFULL on STN
2005:286462 Reshaped human antibody to human medulloblastoma cells.
    Ohtomo, Toshihiko, Gotenba-shi, JAPAN
    Sato, Koh, Gotenba-shi, JAPAN
    Tsuchiya, Masayuki, Gotenba-shi, JAPAN
    CHUGAI SEIYAKU KABUSHIKI KAISHA (non-U.S. corporation)
    US 2005249726 A1 20051110
    APPLICATION: US 2004-839799  A1  20040506 (10)
    PRIORITY: JP 1993-291078  19931119
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. An L chain variable region (V region) of an antibody to human
       medulloblastoma cells, comprising three complementarity determining
       regions (CDRs) having the amino acid sequences defined below:

       CDR1:  Lys Ala Ser Gln Asn Val Gly Thr Asn Val Ala

       CDR2:  Ser Ala Ser Tyr Arg Tyr Ser

       CDR3:  Gln Gln Tyr Asn Ser Tyr Pro Arg Ala or a portion thereof and four
       framework regions (FRs).

       2-39. (canceled)

       40. A method for making a reshaped human antibody comprising:  (a)
       providing complementarity determining regions derived from a mouse
       antibody and framework regions derived from a human antibody,  (b)
       substituting an amino acid residue at position 46 of an L chain numbered
       according to Kabat numbering with a mouse antibody residue to provide a
       functional antigen binding site, and  (c) substituting 0-5 amino acid
       residue(s) on an H chain numbered according to Kabat numbering with a
       mouse antigen binding site.

       41. The method of claim 40, wherein an amino acid residue 94 of H chain
       numbered according to Kabat is an additional mouse antibody residue.

       42. The method of claim 41, wherein amino acid residues 27, 28, 29 and
       30 of H chain numbered according to Kabat numbering are additional mouse
       antibody residues.

       43. The method of claim 40, wherein the amino acid residue 46 is
       proline.

       44. A reshaped human antibody produced by the method of claim 40.

       45. A reshaped human antibody produced by the method of claim 41.

       46. A reshaped human antibody produced by the method of claim 42.

       47. A reshaped human antibody produced by the method of claim 43.

       48. A method for making a single-chain Fv region comprising:  (a)
       producing a reshaped antibody by substituting an amino acid residue at
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position 46 of an L chain V region numbered according to Kabat numbering, as a mouse antigen binding site and by substitution 0-5 amino acids on the H chain V region, numbered according to Kabat numbering, with a mouse antigen binding site, (b) linking the L chain V region and the H chain V region with a **linker** peptide, and (c) combining identified **complementarity determining regions** derived from a mouse antibody and **framework regions** derived from a human antibody, wherein an amino acid residue 46 of L chain V region numbered according to Kabat numbering is a mouse residue and the single chain Fv region creates a functional antigen binding site.

49. The method of claim 48, wherein an amino acid residue 94 of H chain numbered according to Kabat numbering is an additional mouse antibody residue.

50. The method of claim 49, wherein amino acid residues 27, 28, 29 and 30 of H chain numbered according to Kabat numbering are additional mouse antibody residues.

51. The method of claim 48, wherein the amino acid residue 46 is proline.

52. The method of claim 48, wherein the **linker** peptide has the following amino acid sequence:

(SEQ ID NO: 111)
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly

Gly Gly Ser.

53. A single-chain Fv region produced by the method of claim 48.

54. A single-chain Fv region produced by the method of claim 49.

55. A single-chain Fv region produced by the method of claim 50.

56. A single-chain Fv region produced by the method of claim 51.

57. A single-chain Fv region produced by the method of claim 52.

58. A method for making a reshaped human antibody comprising: (a) providing complementary determining regions identified from a mouse antibody and **framework regions** identified from a human antibody, and (b) substituting an amino acid residue of position 46 of an L chain numbered according to Kabat numbering with a mouse antigen binding site and (c) substituting 0-5 amino acid residue(s) on an H chain numbered according to Kabat numbering with a mouse antigen binding site.

59. A method for making a single-chain Fv region comprising: (a) producing a reshaped antibody by substituting an amino acid residue on position 46 of an L chain V region numbered according to Kabat numbering, with a mouse antigen binding site and by substitution 0-5 amino acids of an H chain V region numbered according to Kabat numbering, with a mouse antigen binding site, (b) linking the L chain V region and the H chain V region with a **linker** peptide, and (c) combining identified complementary determining regions from a mouse antibody and **framework regions** identified from a human antibody, wherein an amino acid residue 46 of L chain V region numbered according to Kabat numbering is a mouse residue and the single chain Fv region creates a functional antigen binding site.

L19 ANSWER 2 OF 11 USPATFULL on STN
2005:243015 Murine monoclonal anti-idiotype antibody 11D10 and methods of use thereof.
Chatterjee, Malaya, Lexington, KY, UNITED STATES
Foon, Kenneth A., Lexington, KY, UNITED STATES
Chatterjee, Sunil K., Lexington, KY, UNITED STATES
The Board of Trustees of the University of Kentucky, Lexington, KY, UNITED STATES (U.S. corporation)
US 6949244 B1 20050927
APPLICATION: US 1996-766350 19961213 (8)
PRIORITY: US 1996-35345P 19960129 (60)
US 1995-31306P 19951220 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. An isolated monoclonal anti-idiotype antibody 11D10 produced by hybridoma cell line ATCC No. HB 12020.

2. A labeled antibody comprising the antibody of claim 1, further comprising a wherein said label is capable of producing a detectable signal.

3. A composition comprising the anti-idiotype antibody of claim 1 and a pharmaceutically acceptable excipient.

4. A method for promoting clearance of a labeled anti-human milk fat globule (HMFG) antibody that binds to the antibody of claim 1 from the circulation or tissues of an individual who has received the labeled anti-HMFG antibody, comprising administering monoclonal the antibody of claim 1 to the individual.

5. A method for detecting an anti-human milk fat globule immunological response in an individual comprising the steps of (a) contacting a biological sample from the individual with the monoclonal anti-idiotype antibody 11D10 of claim 1 under conditions that permit formation of a stable complex between the monoclonal anti-idiotype antibody and an antibody containing the paratope of the monoclonal anti-idiotype antibody; and (b) detecting any of the complexes formed, wherein the presence of the complexes is indicative of the presence of an anti-human milk fat globule immunological response in the individual.

6. A composition comprising an effective amount of the anti-idiotype antibody of claim 1, wherein an effective amount is an amount sufficient to elicit an anti-human milk fat globule immune response.

7. An immunogenic composition comprising the anti-idiotype antibody of claim 1 and a pharmaceutically acceptable excipient.

8. The immunogenic composition of claim 7, further comprising an adjuvant.

9. A method of eliciting an immune response in an individual with advanced human milk fat globule associated disease comprising the step of administering an effective amount of the immunogenic composition of claim 8 to the individual.

10. A method of eliciting an immune response in an individual with advanced human milk fat globule associated disease comprising the step of administering an effective amount of the anti-idiotype antibody of claim 1 to the individual.

11. The method of claim 10, wherein the advanced human milk fat globule

associated disease is breast cancer.

12. A kit comprising the anti-idiotype antibody of claim 1 in suitable packaging.

13. The kit of claim 12, wherein the antibody comprises a detectable label.

14. A hybridoma cell line designated ATCC No. HB 12020.

15. A hybridoma having all the identifying characteristics of a cell of the hybridoma cell line according to claim 14.

16. A purified antibody having all the identifying characteristics of antibody produced by a hybridoma cell line according to claim 14.

17. A composition comprising an effective amount of the antibody of claim 16, wherein an effective amount is an amount sufficient to elicit an anti-human milk fat globule immune response.

18. The purified antibody of claim 16, said antibody comprising the sequence of SEQ ID NO:2.

19. The purified antibody of claim 16, said antibody comprising the sequence of SEQ ID NO:4.

20. A composition comprising the purified antibody of claim 16 and a pharmaceutically acceptable excipient.

21. A composition according to claim 20, wherein the composition is immunogenic.

22. A composition according to claim 21, further comprising an adjuvant.

23. A polypeptide having immunological activity of anti-idiotype antibody 11D10, wherein the polypeptide comprises an immunoglobulin variable region containing three light chain **complementarity determining regions** (CDRs) of anti-idiotype antibody 11D10, and an immunoglobulin variable region containing three heavy chain CDRs of anti-idiotype antibody 11D10, wherein anti-idiotype antibody 11D10 is produced by the hybridoma cell line designated ATCC No. HB 12020, and wherein the immunological activity of the polypeptide is an ability to stimulate a specific immune response against human milk fat globule (HMFG).

24. The polypeptide of claim 23, wherein the light chain variable region amino acid sequence is contained in SEQ ID NO:2 and the heavy chain variable region amino acid sequence is contained in SEQ ID NO:4.

25. The polypeptide of claim 23, wherein the polypeptide contains a sequence of at least 2 contiguous amino acids which are identical in forward or reverse orientation to 2 contiguous amino acids of a sequence in human mucin from human milk fat globule (HMFG), wherein said HMFG sequence is contained in SEQ ID NO:33.

26. A polymeric 11D10 polypeptide comprising a plurality of the polypeptide of claim 23.

27. A kit comprising the polypeptide of claim 23 in suitable packaging.

28. A composition comprising an effective amount of the polypeptide of claim 23, wherein an effective amount is an amount sufficient to elicit

an anti-human milk fat globule immune response.

29. A composition comprising the polypeptide of claim 23 and a pharmaceutically acceptable excipient.

30. A method of eliciting an immune response in an individual with advanced human milk fat globule associated disease comprising the step of administering an effective amount of a polypeptide according to claim 23 to the individual.

31. The polypeptide of claim 23, wherein the specific immune response comprises production of HMFG-specific antibodies.

32. The polypeptide of claim 23, wherein the specific immune response comprises production of HMFG-specific T cells.

33. An immunogenic composition comprising the polypeptide of claim 23 and a pharmaceutically acceptable excipient.

34. The immunogenic composition of claim 33, further comprising an adjuvant.

35. A fusion polypeptide comprising the polypeptide of claim 23.

36. A fusion polypeptide according to claim 35, wherein the amino acid sequences of the light chain variable region and the heavy chain variable region are contained in SEQ ID NO:2 and SEQ ID NO:4, respectively.

37. The fusion polypeptide of claim 35 further comprising a cytokine.

38. The fusion polypeptide of claim 37, wherein the cytokine is granulocyte macrophage colony stimulating factor.

39. The fusion polypeptide of claim 37, wherein the cytokine is interleukin 2.

40. The fusion polypeptide of claim 35, wherein the immunoglobulin variable region of the polypeptide of claim 20, containing three CDRs from the light chain variable region of anti-idiotype antibody 11D10, and the immunoglobulin variable region of the polypeptide of claim 20, containing three CDRs from the heavy chain variable region of anti-idiotype antibody 11D10, are linked by a **linker** polypeptide of about 5 to 20 amino acids.

41. A fusion polypeptide according to claim 40, wherein the **linker** polypeptide comprises the amino acid sequence $(GGGGS)_3$ (SEQ ID NO:35).

42. The fusion polypeptide of claim 35, comprising the light chain variable region and the heavy chain variable region of anti-idiotype antibody 11D10, wherein the light chain variable region and the heavy chain variable region are contained in SEQ ID NO:2 and SEQ ID NO:4, respectively.

43. The fusion polypeptide of claim 42, wherein the light chain variable region and the heavy chain variable region are joined by a **linker** polypeptide of about 5 to 20 amino acids.

44. The fusion polypeptide of claim 35 further comprising a heterologous immunoglobulin constant region.

45. The fusion polypeptide of claim 44, wherein the immunoglobulin constant region is human.

46. A humanized antibody comprising three CDRs from the light chain variable region of antibody 11D10, three CDRs from the heavy chain variable region of antibody 11D10, and a constant region that is a human sequence, wherein antibody 11D10 is produced by the hybridoma cell line designated ATCC No. HB 12020, and wherein the humanized antibody is able to stimulate a specific immune response against human milk fat globule (HMFG).

47. The humanized antibody of claim 46, wherein the specific immune response comprises production of HMFG-specific antibody.

48. The humanized antibody of claim 46, wherein the specific immune response comprises production of HMFG-specific T cells.

49. The humanized antibody of claim 46, wherein the **framework regions** are human sequences.

50. A humanized antibody according to claim 46, wherein the light chain variable region of antibody 11D10 and the heavy chain variable region of antibody 11D10 are contained in SEQ ID NO:2 and SEQ ID NO:4, respectively.

51. A composition comprising the humanized antibody of claim 46 and a pharmaceutically acceptable excipient.

52. A method of eliciting an immune response in an individual with advanced human milk fat globule associated disease comprising the step of administering an effective amount of an antibody according to claim 46 to the individual.

53. A composition according to claim 51, wherein the composition is immunogenic.

54. A composition according to claim 53 further comprising an adjuvant.

55. A composition comprising a pharmaceutically acceptable excipient and a polypeptide having immunological activity of anti-idiotype antibody 11D10, wherein the polypeptide comprises an immunoglobulin variable region containing three light chain **complementarity determining regions** (CDRs) of anti-idiotype antibody 11D10, and an immunoglobulin variable region containing three heavy chain CDRs of anti-idiotype antibody 11D10, wherein anti-idiotype antibody 11D10 is produced by the hybridoma cell line designated ATCC No. HB 12020, and wherein the immunological activity of the polypeptide is an ability to stimulate a specific immune response against human milk fat globule (HMFG).

56. The composition of claim 55, wherein the specific immune response comprises production of HMFG-specific antibody.

57. The composition of claim 55, wherein the specific immune response comprises production of HMFG-specific T cells.

58. A humanized antibody comprising three CDRs from the light chain variable region of antibody 11D10, three CDRs from the heavy chain variable region of antibody 11D10, and **framework regions** that are human sequences, wherein antibody 11D10 is produced by the hybridoma cell line designated ATCC No. HB 12020, and wherein the humanized antibody is able to stimulate a specific immune response against human milk fat globule (HMFG).

59. A method of eliciting an immune response in an individual with advanced human milk fat globule associated disease comprising the step of administering an effective amount of an antibody according to claim 58 to the individual.

60. A humanized antibody comprising three CDRs from the light chain variable region of antibody 11D10, three CDRs from the heavy chain variable region of antibody 11D10, and **framework regions** that are human sequences, wherein antibody 11D10 is produced by the hybridoma cell line designated ATCC No. HB 12020, wherein the humanized antibody is able to stimulate a specific immune response against human milk fat globule (HMFG), and wherein the light chain variable region of antibody 11D10 and the heavy chain variable region of antibody 11D10 are contained in SEQ ID NO:2 and SEQ ID NO:4, respectively.

61. A method of eliciting an immune response in an individual with advanced human milk fat globule associated disease comprising the step of administering an effective amount of an antibody according to claim 60 to the individual.

62. A composition comprising the humanized antibody of claim 60 and a pharmaceutically acceptable excipient.

63. A composition according to claim 62, wherein the composition is immunogenic.

64. A composition according to claim 63, further comprising an adjuvant.

65. An antibody comprising a light chain variable region amino acid sequence contained in SEQ ID NO:2 and a heavy chain variable region amino acid sequence contained in SEQ ID NO:4, wherein the antibody is able to stimulate a specific immune response against human milk fat globule (HMFG).

66. A composition comprising the antibody of claim 65 and a pharmaceutically acceptable excipient.

67. A composition according to claim 66, wherein the composition is immunogenic.

68. A composition according to claim 67, further comprising an adjuvant.

69. An isolated antibody comprising three CDRs from the light chain variable region of anti-idiotype antibody 11D10 and three CDRs from the heavy chain variable region of anti-idiotype antibody 11D10, wherein anti-idiotype antibody 11D10 is produced by the hybridoma cell line designated ATCC No. HB 12020, wherein the CDRs from the light chain variable region are contained in SEQ ID NO:2 and the CDRs from the heavy chain variable region are contained in SEQ ID NO:4, and wherein the antibody is able to stimulate a specific immune response against human milk fat globule (HMFG).

70. A method of eliciting an immune response in an individual with advanced human milk fat globule associated disease comprising the step of administering an effective amount of an antibody according to claim 69 to the individual.

71. A composition comprising the antibody of claim 69 and a pharmaceutically acceptable excipient.

72. A composition according to claim 71, wherein the composition is

immunogenic.

73. A composition according to claim 72, further comprising an adjuvant.

74. A polypeptide comprising an immunoglobulin variable region containing three light chain **complementarity determining regions** (CDRs) of antibody 11D10, or an immunoglobulin variable region containing three heavy chain CDRs of antibody 11D10, wherein antibody 11 D10 is produced by a hybridoma cell line designated ATCC NO. HB 12020.

75. A composition comprising the polypeptide of claim 74 and a pharmaceutically acceptable excipient.

76. A polypeptide according to claim 74, comprising an immunoglobulin variable region containing the three light chain CDRs of antibody 11D10.

77. A polypeptide according to claim 74, comprising an immunoglobulin variable region containing the three heavy chain CDRs of antibody 11D10.

78. A polypeptide according to claim 74, wherein the light chain variable region is contained in SEQ ID NO:2.

79. A polypeptide according to claim 74, wherein the heavy chain variable region is contained in SEQ ID NO:4.

80. A polypeptide comprising an immunoglobulin variable region containing three light chain **complementarity determining regions** (CDRs) of antibody 11D10 and an immunoglobulin variable region containing three heavy chain CDRs of antibody 11D10, wherein antibody 11D10 is produced by a hybridoma cell line designated ATCC NO. HB 12020, and wherein the light and heavy chain variable region sequences are contained in SEQ ID NO:2 and SEQ ID NO:4, respectively, and wherein the antibody is able to stimulate a specific immune response against human milk fat globule (HMFG).

81. A method of eliciting an immune response in an individual with advanced human milk fat globule associated disease comprising thee step of administering an effective amount of a polypeptide according to claim 80 to the individual.

L19 ANSWER 3 OF 11 USPATFULL on STN
2005:227639 Methods of treating thrombotic diseases with von willebrand factor specific antibodies.
Co, Man Sung, Cupertino, CA, UNITED STATES
Vasquez, Maximiliano, Palo Alto, CA, UNITED STATES
Ajinomoto Co., Inc., Tokyo, JAPAN (non-U.S. corporation)
US 2005197494 A1 20050908
APPLICATION: US 2005-66262 A1 20050228 (11)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1-21. (canceled)

22. A method of treating a patient having or at risk of a thrombotic disease or atherosclerosis, comprising: administering to said patient an effective dose of a humanized immunoglobulin, wherein said humanized immunoglobulin comprises (a) **complementarity determining regions** having amino acid sequences RFWMS (residues 49-53 of SEQ ID NO: 6), EVNPDNNTMNYTPSLKD (residues 68-84 of SEQ ID NO: 6) and PPYYGSYGGFAY (residues 117-128 of SEQ ID NO: 6), in the heavy chain, and RASENIYNNLA (residues 44-54 of SEQ ID NO: 8), AATNLAD (residues 70-76 of SEQ ID NO:

8) and GHLWTSPYT (residues 109-117 of SEQ ID NO: 8), in the light chain, and (b) **framework regions** of human antibody, wherein the **framework region** in the heavy chain is at least 85% homologous to SEQ ID NO: 6 and the **framework region** in the light chain is at least 85% homologous to SEQ ID NO: 8.

23. The method of claim 22, wherein the treatment is for stroke, transient ischemic attack, unstable angina, acute myocardial infarction, peripheral vascular disease, deep vein thrombosis, hemolytic uremic syndrome, hemolytic anemia, acute renal failure, thrombotic thrombocytopenic purpura, ischemic complications caused by acute and subacute thrombosis, restenosis after endovascular intervention or preventing ischemic complications caused by reocclusion after thrombolytic treatment in acute myocardial infarction as an adjunctive therapy.

24. The method of claim 22, wherein the immunoglobulin is a Fab, a F(ab')2, or a Fv.

25. The method of claim 22, wherein the immunoglobulin is a single chain antibody produced by joining VL and VH with a DNA **linker**.

26. The method of claim 22, wherein the immunoglobulin has an IgG2 or IgG4 immunoglobulin subtype.

27. The method of claim 22, wherein the **framework region** is a Cγ2 or Cγ4 region.

28. The method of claim 22, wherein the immunoglobulin is admixed with a pharmaceutically acceptable carrier.

L19 ANSWER 4 OF 11 USPATFULL on STN
2005:43692 Immunoglobulin having particular framework scaffold and methods of making and using.
Zhang, Mei-Yun, Frederick, MD, UNITED STATES
Schillberg, Stefan, Aachen, GERMANY, FEDERAL REPUBLIC OF
Zimmermann, Sabine, Koeln, GERMANY, FEDERAL REPUBLIC OF
Fiore, Stefano di, Neubrandenburg, GERMANY, FEDERAL REPUBLIC OF
Emans, Neil, Thiminster-clermont, BELGIUM
Fischer, Rainer, Monschau, GERMANY, FEDERAL REPUBLIC OF
US 2005037420 A1 20050217
APPLICATION: US 2004-489328 A1 20040827 (10)
WO 2002-US29003 20020913
PRIORITY: US 2001-318904P 20010914 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An immunoglobulin molecule comprising one or more heavy chain **framework regions**, HFR1, HFR2, HFR3, and HFR4, and one or more light chain **framework regions**, LFR1, LFR2, LFR3 and LFR4, and further comprising **complementarity determining regions**, CDR-H1, CDR-H2, CDR-H3, and/or CDR-L1, CDR-L2 and CDR-L3, said immunoglobulin molecule having the structure: (a) HFR1--CDR-H1--HFR2--CDR-H2--HFR3--CDR-H3--HFR4 or (b) LFR1--CDR-L1--LFR27-CDR-L2--LFR3--CDR-L3--LFR4, or (a) and (b) wherein, (i) HFR1 is a first **framework region** in (b) consisting of a sequence of about 30 amino acid residues; (ii) HFR2 is a second **framework region** in (b) consisting of a sequence of about 14 amino acid residues; (iii) HFR3 is a third **framework region** in (b) consisting of a sequence of about 29 to about 32 amino acid residues; (iv) HFR4 is a **framework region** of (b) consisting of a sequence of 7 to about 9 amino acid residues, wherein the first amino acid residue is

tryptophan (Trp); (v) CDR-H1 is a first complementary determining region; (vi) CDR-H2 is a second complementary determining region; (vii) CDR-H3 is a third complementary determining region; (viii) LFR1 is a first **framework region** consisting of a sequence of about 22 to about 23 amino acid residues; (ix) LFR2 is a second **framework region** consisting of a sequence of about 13 to about 16 amino acid residues, wherein a Pro or Leu must be at position 10 if the sequence is 15 amino acid residues long or position 11 if the sequence is 16 amino acid residues long; (x) LFR3 is a third **framework region** consisting of a sequence of about 32 amino acid residues; (xi) LFR4 is a fourth **framework region** consisting of a sequence of about 12 to about 13 amino acid residues, wherein the first amino acid residue is Phe; (xii) CDR-L1 is a first complementary determining region; (xiii) CDR-L2 is a second complementary determining region; (xiv) CDR-L3 is a third complementary determining region, wherein the length of the CDRs and the **framework regions** and positions of the amino acid residues in the CDRs and the **framework regions** are in accordance with the Kabat numbering system.

2. The immunoglobulin molecule of claim 1 wherein the HFR3 consists of 29-32 amino acid residues, wherein the first amino acid residue is Arginine (Arg) and the tenth amino acid residue is glutamine (Gln).

3. The immunoglobulin molecule of claim 1, comprising a CDR-H1 consisting of about 5 to about 7 amino acid residues, a CDR-H2 consisting of about 16 to about 18 amino acid residues, CDR-H3 consisting of about 9 to about 21 amino acid residues, a CDR-L1 consisting of about 5 to about 14, CDR-L2 consisting of about 5 to about 7 amino acid residues, CDR-L3 consisting of about 5 to about 15 amino acid residues, LFR1 consists of about 22 amino acid residues, LFR2 consists of about 16 amino acid residues, LFR3 consists of 32 amino acid residues and LFR4 consists of about preferably about 13 amino acid residues.

4. The immunoglobulin molecule of claim 3 wherein the CDR-H1 consists of about 5 amino acid residues, the CDR-H2 consists of about 17 amino acid residues, the CDR-H3 consists of 9 to about 19 amino acid residues, the CDR-L1 consists of 8, 9, 10 or 13 amino acid residues, the CDR-L2 consists of 7 amino acid residues and the CDR-L3 consists of about 8 to about 12 amino acid residues.

5. The immunoglobulin molecule of claim 4, wherein the CDR-H3 consist of about 14 amino acid residues to about 19 amino acid residues.

6. An immunoglobulin molecule of claim 1 wherein said at least one of said heavy chain **framework regions** is selected from the group consisting of an HFR1 comprising SEQ ID NO: 1, an HFR2 comprising SEQ ID NO: 2, an HFR3 comprising SEQ ID NO: 3, and an HFR4 comprising SEQ ID NO: 4, and wherein at least one of said light chain **framework regions** is selected from the group consisting of an LFR1 comprising SEQ ID NO: 5, an LFR2 comprising SEQ ID NO: 6, an LFR3 comprising SEQ ID NO: 7 and an LFR4 comprising SEQ ID NO: 8.

7. The immunoglobulin molecule of claim 1, wherein: HFR1 comprises SEQ ID NO: 1; HFR2 comprises SEQ ID NO: 2; HFR3 comprises SEQ ID NO: 3; HFR4 comprises SEQ ID NO: 4; LFR1 comprises SEQ ID NO: 5; LFR2 comprises SEQ ID NO: 6; LFR3 comprises SEQ ID NO: 7, and; LFR4 comprises SEQ ID NO: 8.

8. The immunoglobulin of claim 7 wherein amino acid residue at positions 18, 19 or 20 in SEQ ID NO: 3 are absent and are not substituted by any other amino acid.

9. The immunoglobulin of claim 7 wherein the amino acid residue at position 6 in SEQ ID NO:6 is absent and is not substituted by any other amino acid.

10. The immunoglobulin of claim 7 wherein amino acid residue at position 10 in SEQ ID NO: 8 is absent and not substituted by any other amino acid.

11. The immunoglobulin of claim 1 wherein the immunoglobulin molecule comprises: (a) HFR1 consisting of SEQ ID NO:1, HFR2 consisting of SEQ ID NO:2, HFR3 consisting of SEQ ID NO:3, and HFR4 consisting of SEQ ID NO:4, or (b) LFR1 consisting of SEQ ID NO:5, LFR2 consisting of SEQ ID NO:6, LFR3 consisting of SEQ ID NO:7 and LFR4 consisting of SEQ ID NO: 8, or variants of (a) or (b) having conservative substitutions in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7 or 8.

12. The immunoglobulin of claim 11 wherein: CDR-L1 is 5-14 amino acid residues in length, CDR-L2 is 5-7 amino acid residues in length, CDR-L3 is 5-15 amino acid residues in length CDR-H1 is 5-8 amino acid residues in length, CDR-H2 is 16-18 amino acid residues in length, and CDR-H3 is 9-19 amino acid residues in length.

13. The immunoglobulin molecule of claim 1 further comprising a cellular targeting signal and/or a tag.

14. The immunoglobulin molecule of claim 1 wherein said cellular targeting signal is selected from the group consisting of apoplastic targeting peptide, an endoplasmic reticulum targeting peptide, a vacuole targeting peptide, protein body targeting peptide and a chloroplast targeting peptide.

15. The isolated immunoglobulin molecule of claim 1 having an amino acid sequence comprising: (a) HFR1 consisting of SEQ ID NO:1, HFR2 consisting of SEQ ID NO:2, HFR3 consisting of SEQ ID NO:3, and HFR4 consisting of SEQ ID NO:4, and (b) LFR1 consisting of SEQ ID NO:5, LFR2 consisting of SEQ ID NO:6, LFR3 consisting of SEQ ID NO:7 and LFR4 consisting of SEQ ID NO: 8, wherein (i) CDR-H1 consists of about 5 to about 7 amino acid residues, (ii) CDR-H2 consists of about 16 to about 18 amino acid residues, (iii) CDR-H3 consists of about 9 to about 21 amino acid residues, (iv) CDR-L1 consists of about 5 to about 14, (v) CDR-L2 consists of about 5 to about 7 amino acid residues, (vi) CDR-L3 consists of about 5 to about 15 amino acid residues.

16. The isolated immunoglobulin molecule of claim 15 wherein: CDR-H1 consists of about 5 amino acid residues, CDR-H2 consists of about 17 amino acid residues, CDR-H3 consists of 9 to about 19 amino acid residues, CDR-L1 consists of 8, 9, 10 or 13 amino acid residues, CDR-L2 consists of 7 amino acid residues and CDR-L3 consists of about 8 to about 12 amino acid residues.

17. The immunoglobulin molecule of claim 16 wherein CDR-H3 consists of about 14 to about 19 amino acid residues.

18. The immunoglobulin molecule of claim 1, 11 or 15 further comprising a **linker** which joins (a) to (b).

19. A composition comprising the immunoglobulin molecule of the claim 1.

20. The composition of claim 19, wherein said composition is a plant composition.

21. A population of isolated immunoglobulin molecules produced by, (a) expressing a plurality of nucleic acid molecules encoding the immunoglobulin molecules of claim 1 in a host cell, to produce a population of immunoglobulin molecules, and (b) isolating the expressed population of immunoglobulin molecules.

22. An isolated nucleic acid molecule encoding the immunoglobulin molecule of claim 1.

23. The isolated nucleic acid molecule of claim 22 comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO; 13 and SEQ ID NO; 14.

24. An isolated nucleic acid molecule encoding an immunoglobulin molecule variable domain **framework region** wherein said **framework region** comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO:8.

25. The isolated nucleic acid molecule of claim 21 wherein said immunoglobulin molecule comprises: (a) an immunoglobulin heavy chain variable domain comprising **framework regions** SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4, or (b) an immunoglobulin light chain variable domain comprising **framework regions** SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO:8.

26. A recombinant library comprising one or more isolated nucleic acid molecule of claim 22.

27. A vector comprising an isolated nucleic acid molecule of claim 22 in operable linkage with a promoter.

28. The vector of claim 27, wherein the promoter is selected from a group consisting of a tissue specific, an inducible, a constitutive, a developmentally regulated and a temporally regulated promoter.

29. The vector of claim 28 wherein the tissue specific promoter is a seed specific promoter, root specific promoter or leaf specific promoter.

30. The vector of claim 28, wherein the seed specific promoter is a glutelin-1 promoter.

31. The vector of claim 28, wherein the inducible promoter is an auxin inducible promoter, a heat shock inducible promoter, a light inducible promoter or a wounding inducible promoter.

32. The vector of claim 28, wherein the constitutive promoter is a cauliflower mosaic virus 35s promoter or an ubiquitin promoter.

33. The vector of claim 28, wherein the developmentally regulated promoter is an alpha tubulin promoter or a soybean SbPRP1 promoter.

34. The vector of claim 27 comprising a nucleotide sequence encoding a cellular targeting peptide.

35. The vector of claim 34, wherein the cellular targeting peptide is an apoplastic targeting peptide, an endoplasmic reticulum targeting peptide, a vacuole targeting peptide, a chloroplast targeting peptide and a protein body targeting peptide.

36. A host cell comprising a nucleic acid molecule of claim 22.

37. The host cell of claim 36 wherein said host is bacterial cell, a yeast cell, an algae cell, an insect cell, a mammalian cell or a plant cell.

38. The host cell of claim 35, wherein the nucleic acid molecule encoding the immunoglobulin molecule is in operable linkage with a promoter.

39. The host cell of claim 36 wherein said host cell is a is monocotyledonous plant cell.

40. The host cell of claim 36, wherein said host cell is a dicotyledonous plant cell.

41. The host cell of claim 39, wherein the monocotyledonous plant is selected from the group consisting of amaranth, barley, maize, oat, rice, sorghum and wheat.

42. The host cell of claim 40, wherein the dicotyledonous plant is selected from the group consisting of tobacco, tomato, ornamentals, potato, sugarcane, soybean, cotton, canola, alfalfa and sunflower.

43. The host cell of claim 37 wherein said host cell is selected from the group consisting of E. coli cells, CHO cells, and COS cells.

44. A method for generating a recombinant library of nucleic acid molecules encoding immunoglobulin molecules having identical **framework regions** wherein said immunoglobulins accumulate to high levels in a host cell, said method comprising the steps of (a) introducing a population of nucleic acid molecules encoding immunoglobulin molecules comprising avian **framework regions** into host cells to generate transformed host cells, (b) assaying said transformed host cells for expression of said nucleic acid molecules, (c) identifying transformed host cells producing levels of immunoglobulin molecules that are at least 0.15% of total cellular protein, (d) isolating the immunoglobulin-encoding nucleic acid molecules from the transformed host cells identified in (c), (e) determining the amino acid sequence of **framework regions** of the immunoglobulin molecules encoded by the nucleic acid molecules of (d) (f) identifying which amino acid residue positions in the **framework regions** of (e) are conserved among the immunoglobulin molecules, (g) preparing a consensus sequence for the **framework regions** of (d) having the conserved amino acid residues identified in (f) (h) preparing one or more nucleic acid molecules encoding immunoglobulin molecules having the **framework regions** of (g) and **complementarity determining regions** (CDRs) to form a recombinant library of nucleic acid molecules encoding immunoglobulin molecules having identical **framework regions**

45. The method of claim 44, wherein the immunoglobulin molecule comprises CDRs of an avian, piscean or mammalian antibody.

46. The method of claim 45, wherein the mammalian antibody is a camelid, murine or human antibody.

47. The method of claim 44, wherein the immunoglobulin molecules are selected from the group consisting of immunoglobulin heavy chain or light chain variable domains (V_L or V_H), scFv, diabodies, triabodies and tetrabodies.

48. The method of claim 44, wherein the nucleic acid molecules in (f)

comprise randomized CDR-encoding sequences.

49. A method for identifying nucleic acid molecules of claim 44(f) that encode an immunoglobulin that binds to a preselected antigen comprising expressing said nucleic acid molecules to produce an immunoglobulin, assaying the binding of said immunoglobulin to the preselected antigen and identifying the nucleic acid molecule that encodes the immunoglobulin that binds to said preselected antigen.

50. The method of claim 44, wherein the isolated nucleic acid molecule of step (a) further comprises a nucleotide sequence that encodes a cellular targeting peptide, such that said nucleic acid molecule of step (a) encodes a fusion of the immunoglobulin molecule and the cellular targeting peptide.

51. The method of claim 44, wherein steps (a) through (h) may be repeated.

52. A method for producing a plant resistant to a pathogen comprising transforming a plant cell with a nucleic acid molecule of claim 19 wherein said nucleic acid encodes an immunoglobulin molecule that is a specific for said pathogen (a) regenerating a plant from said transformed cells, and (b) growing said regenerated plant, under conditions which promote expression of said nucleic acid molecule, wherein expression of said nucleic acid molecule confers resistance to said pathogen.

53. The method of claim 52, wherein the pathogen is a virus, a bacteria, a mycoplasm, a fungus, a nematode or an insect.

54. A method for preparing a recombinant library expressing immunoglobulin molecules or domains thereof which comprise (a) a heavy chain variable domain having the structure HFR1--CDR-H1--HFR2--CDR-H2--HFR3--CDR-H3--HFR4 and/or (b) a light chain variable domain having the structure LFR1--CDR-L1--LFR2--CDR-L2--LFR3--CDR-L3--LFR4, wherein (i) HFR1 is a first **framework region** in (b) consisting of a sequence of about 30 amino acid residues; (ii) HFR2 is a second **framework region** in (b) consisting of a sequence of about 14 amino acid residues; (iii) HFR3 is a third **framework region** in (b) consisting of a sequence of about 29 to about 32 amino acid residues, wherein the first amino acid residue is Arginine (Arg) and the tenth amino acid residue is either leucine (Leu) or proline (Pro); (iv) HFR4 is a **framework region** of (b) consisting of a sequence of 7 to about 9 amino acid residues wherein the first amino acid residue is tryptophan (Trp); (v) CDR-H1 is a first complementary determining region, (vi) CDR-H2 is a second complementary determining region; (vii) CDR-H3 is a third complementary determining region; (viii) LFR1 is a first **framework region** consisting of a sequence of about 22 to about 23 amino acid residues; (ix) LFR2 is a second **framework region** consisting of a sequence of about 13 to about 16 amino acid residues; (x) LFR3 is a third **framework region** consisting of a sequence of about 32 amino acid residues; (xi) LFR4 is a fourth **framework region** consisting of a sequence of about 12 to about 13 amino acid residues wherein the first amino acid residue is Phe; (xii) CDR-L1 is a first complementary determining region; (xiii) CDR-L2 is a second complementary determining region; (xiv) CDR-L3 is a third complementary determining region, wherein said method comprises preparing one or more nucleic acid molecules encoding the immunoglobulin molecules, or domains thereof, and expressing said nucleic acid molecules in an appropriate host cell wherein expression of said nucleic acid produces a recombinant library expressing the immunoglobulin molecules or the domains thereof.

55. A method for identifying an immunoglobulin molecule of the recombinant library of claim 54 which binds to a predetermined antigen comprising contacting the immunoglobulin molecules with the predetermined antigen and assaying for binding therebetween.

56. The method of claim 55 further comprising identifying the nucleic acid molecule that encodes the immunoglobulin molecule or domain thereof identified in claim 56.

57. A method for preparing a transgenic plant comprising one or more immunoglobulin molecule, comprising: (a) introducing a nucleic acid molecule of claim 20 into a plant cell to generate a transformed plant cell; (b) regenerating a transgenic plant from said transformed plant cell; and growing said transgenic plant under conditions suitable for production of said immunoglobulin molecule from said nucleic acid molecule.

58. The method of claim 57 wherein the immunoglobulin molecule is an avian derived immunoglobulin molecule.

59. A transgenic plant produced by the method of claim 57, wherein the immunoglobulin molecule is a VL, VH, scFv, diabody, triabody or tetrabody.

60. A seed of the transgenic plant of claim 57.

61-67. (Cancelled)

68. A method for producing an immunoglobulin molecule having a chimeric variable domain comprising: (a) determining amino acid sequence of an avian immunoglobulin molecule comprising a variable domain, wherein said variable domain contains **framework regions**, and complementary determining regions (CDRs) and determining amino acid sequence of a preselected immunoglobulin molecule, which is specific for an antigen, said preselected immunoglobulin comprising a variable domain which contains **framework regions** and CDRs, wherein the **framework regions** and CDRs of the immunoglobulin molecules are in accordance with Kabat's numbering system, (b) comparing the amino acid sequences of the variable domains of the avian immunoglobulin and the preselected immunoglobulin to identify differences in amino acid residues at corresponding positions in the avian and preselected antibody **framework regions** and CDRs that are necessary for maintaining conformation of the CDRs, (c) preparing a nucleic acid molecule encoding an immunoglobulin molecule comprising a variable domain where the variable domain CDRs are the CDRs of the preselected immunoglobulin molecule and wherein the variable domain **framework regions** are the avian **framework regions** with the proviso that one or more of the amino acid residue positions identified in (b) as having different amino acid residues in the avian immunoglobulin molecule variable domain as compared to the preselected immunoglobulin molecule variable domain, contain the amino acid residue present in the preselected immunoglobulin variable domain, and (d) expressing the nucleic acid molecule of (c) to produce an immunoglobulin molecule having a chimeric variable domain.

69. The method of claim 68 wherein the avian immunoglobulin molecule accumulates in a host cell at least about 0.15% total soluble protein.

70. The method of claim 68 wherein the avian immunoglobulin amino acid sequence comprises SEQ ID NO: 51.

71. The method of claim 68 wherein the amino acid residue position which are necessary for maintaining conformation of the CDRs of the

preselected immunoglobulin molecule are determined by the methods of Kabat, Chothia and the contact method.

72. The method of claim 68 wherein the immunoglobulin having a chimeric variable domain is a VL, VH, scFv, diabody, triabody or tetrabody.

L19 ANSWER 5 OF 11 USPATFULL on STN
2004:270071 Antibodies, including FV molecules, and immunoconjugates having high binding affinity for mesothelin and methods for their use.
Pastan, Ira H., Potomac, MD, United States
Chowdhury, Partha S., Rockville, MD, United States
The United States of America as represented by the Secretary of the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 6809184 B1 20041026
WO 9928471 19990610
APPLICATION: US 2000-581345 20000927 (9)
WO 1998-US25270 19981125
PRIORITY: US 1997-67175P 19971201 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. An isolated anti-mesothelin antibody comprising a variable heavy ("VH") chain and a variable light ("VL") chain, which VH and VL chains have complimentarity-determining regions ("CDRs") as set forth in FIG. 1 (SEQ ID NO:5).

2. An antibody of claim 1, wherein said VH and VL chains comprise **framework regions** ("FRs") as set forth in FIG. 1 (SEQ ID NO:5).

3. An antibody of claim 1, wherein said antibody is a single chain Fv ("scFv").

4. An antibody of claim 3, wherein said scFv has VH and VL chains joined by a peptide **linker**.

5. An antibody of claim 4, wherein said peptide **linker** has the sequence of SEQ ID NO:6.

6. An scFv of claim 3, wherein said scFv has the sequence shown in FIG. 1 (SEQ ID NO:5).

7. An antibody of claim 1, which is a disulfide stabilized Fv ("dsFv").

8. A dsFv of claim 7, comprising a VL chain paired with a VH chain, said chains being connected through a disulfide bond between a pair of cysteines, said pair of cysteines being positioned in the respective chains at positions selected from the group consisting of:
VH44-VL100; VH105-VL43; VH105-VL42;
VH44-VL101; VH106-VL43; VH104-VL43;
VH44-VL99; VH45-VL98; VH46-VL98;
VH103-VL43; VH103-VL44, such positions being determined in accordance with the numbering scheme of Kabat and Wu.

9. An antibody of claim 1, wherein said VH and VL chains are encoded by SEQ ID NO:1.

10. An antibody of claim 1, further wherein said antibody is labeled with a detectable label.

11. An scFv of claim 3, further wherein said scFv is labeled with a detectable label.

12. A dsFv of claim 7, which dsFv is labeled with a detectable label.

13. An antibody of claim 1, further wherein said antibody is attached or fused to a therapeutic agent.

14. An scFv of claim 3, further wherein said scFv is attached or fused to a therapeutic agent.

15. A dsFv of claim 7, further wherein said dsFv is attached or fused to a therapeutic agent.

16. An antibody of claim 13, wherein said therapeutic agent is a toxin.

17. An scFv of claim 14, wherein said therapeutic agent is a toxin.

18. A dsFv of claim 15, further wherein said therapeutic agent is a toxin.

19. An antibody of claim 16, wherein said toxin is a Pseudomonas exotoxin or cytotoxic fragment or mutant thereof.

20. An scFv of claim 17, wherein said toxin is a Pseudomonas exotoxin or cytotoxic fragment or mutant thereof.

21. A dsFv of claim 18, wherein said toxin is a Pseudomonas exotoxin or cytotoxic fragment or mutant thereof.

22. An isolated anti-mesothelin antibody comprising a variable heavy ("VH") chain which VH chain has **complementarity-determining regions** as set forth in FIG. 1 (SEQ ID NO:5).

23. An antibody of claim 22, wherein said VH chain has the sequence set forth in FIG. 1 (SEQ ID NO:5).

24. An antibody of claim 22, wherein said antibody is attached or fused to a therapeutic agent or detectable label.

25. An antibody of claim 22, wherein said therapeutic agent is a toxin.

26. An antibody of claim 25, wherein said toxin is a Pseudomonas exotoxin or cytotoxic fragment or mutant thereof.

27. An isolated anti-mesothelin antibody comprising a variable light ("VL") chain which VL chain has **complementarity-determining regions** as set forth in FIG. 1 (SEQ ID NO:5).

28. An antibody of claim 27, wherein said VL chain has the sequence set forth in FIG. 1 (SEQ ID NO:5).

29. An antibody of claim 27, wherein said antibody is attached or fused to a therapeutic agent or detectable label.

30. An antibody of claim 29, wherein said therapeutic agent is a toxin.

31. An antibody of claim 30, wherein said toxin is a Pseudomonas exotoxin or cytotoxic fragment or mutant thereof.

32. A composition comprising a pharmaceutically acceptable carrier and an immunoconjugate which comprises a therapeutic agent or a detectable

label attached or fused to an anti-mesothelin antibody comprising a variable heavy ("VH") chain and a variable light ("VL") chain, which VH and VL chains have complementary-determining regions ("CDRs") as set forth in FIG. 1 (SEQ ID) NO:5).

33. A composition of claim 32, wherein said VH and VL chains comprise **framework regions** ("FRs") as shown in FIG. 1 (SEQ ID NO:5).

34. A composition of claim 32, wherein said antibody is a single chain Fv ("scFv").

35. A composition of claim 34, wherein said scFv has VH and VL chains joined by a peptide **linker**.

36. A composition of claim 32, wherein said peptide **linker** has the sequence of SEQ ID NO:6.

37. A composition of claim 34, wherein said scFv has the sequence shown in FIG. 1 (SEQ ID NO:5).

38. A composition of claim 32, wherein said antibody is a disulfide stabilized Fv ("dsFv").

39. A composition of claim 32, wherein said therapeutic agent is a toxin.

40. A composition of claim 39, wherein said toxin is a modified Pseudomonas exotoxin or a cytotoxic fragment or mutant thereof.

41. A composition comprising a pharmaceutically acceptable carrier and an immunoconjugate which comprises a therapeutic agent or a detectable label attached or fused to an anti-mesothelin antibody comprising a variable heavy ("VH") chain having **complementarity-determining regions** ("CDRs") as set forth in FIG. 1 (SEQ ID NO:5).

42. A composition of claim 41, wherein said VH chain comprises **framework regions** ("FRs") as set forth in FIG. 1 (SEQ ID NO:5).

43. A composition of claim 41, wherein said therapeutic agent is a toxin.

44. A composition of claim 41, wherein said toxin is a modified Pseudomonas exotoxin or a cytotoxic fragment or mutant thereof.

45. A composition comprising a pharmaceutically acceptable carrier and an immunoconjugate which comprises a therapeutic agent or a detectable label attached or fused to an anti-mesothelin antibody comprising a variable light ("VL") chain having **complementarity-determining regions** ("CDRs") as set forth in FIG. 1 (SEQ ID NO:5).

46. A composition of claim 45, wherein said VL chain comprises **framework regions** ("FRs") as set forth in FIG. 1 (SEQ ID NO:5).

47. A composition of claim 45, wherein said therapeutic agent is a toxin.

48. A composition of claim 45, wherein said toxin is a modified Pseudomonas exotoxin or a cytotoxic fragment or mutant thereof.

49. A kit for detecting mesothelin on the surface of cells, said kit comprising: (i) anti-mesothelin antibody comprising a variable heavy (VH) chain and a variable light ("VL") chain, which VH

and VL chains have **complementarity-determining regions** ("CDRs") as set forth in FIG. 1 (SEQ ID NO:5); and, (ii) instructions printed on a tangible medium, said instructions describing methods of using and said antibody for detecting mesothelin on the surface of cells.

50. A kit of claim 49, wherein said VH and VL chains of said antibody have the sequence set forth in FIG. 1 (SEQ ID NO:5).

51. A kit of claim 49, wherein said antibody is a scFv.

52. A kit of claim 51, wherein said scFv has the sequence set forth in SEQ ID NO:5.

L19 ANSWER 6 OF 11 USPATFULL on STN
2004:70102 Endoglin-specific polypeptide, production and use thereof.
Kontermann, Roland, Ebsdorfergrund, GERMANY, FEDERAL REPUBLIC OF
Miller, Daniel, Dossenheim, GERMANY, FEDERAL REPUBLIC OF
Muller, Rolf, Marburg, GERMANY, FEDERAL REPUBLIC OF
US 2004053329 A1 20040318
APPLICATION: US 2003-363349 A1 20030801 (10)
WO 2001-EP10197 20010904
PRIORITY: DE 2000-10043481 20000904
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A polypeptide, which binds specifically to the extracellular domain of the human endoglin (CD105) protein, characterised in that the polypeptide contains one or more sequences according to SEQ ID No. 1.

2. The polypeptide as claimed in claim 1, characterised in that the polypeptide contains one or more sequences according to SEQ ID No. 2.

3. The polypeptide as claimed in claim 1, characterised in that the polypeptide contains one or more amino acid domains of a human antibody, said amino acid domains being selected from the **framework region** 1 (FR-1), FR-2, FR-3, FR-4, and/or the **complementarity determining region** 1 (CDR-1) and CDR-2 of the antibody.

4. The polypeptide as claimed in claim 1, characterised in that the polypeptide contains one or more amino acid domains with a sequence according to SEQ ID No. 3.

5. The polypeptide as claimed in claim 1, characterised in that the polypeptide contains one or more amino acid domains with a sequence according to SEQ ID No. 4.

6. The polypeptide as claimed in any of claims 3 to 5, characterised in that a peptide **linker** is disposed in each case between the amino acid domains.

7. The polypeptide as claimed in claim 6, characterised in that the peptide **linker** contains a sequence according to SEQ ID No. 5.

8. The polypeptide as claimed in claim 1, characterised in that the polypeptide contains one or more secretion signal sequences.

9. The polypeptide as claimed in claim 8, characterised in that the secretion signal sequence contains a sequence according to SEQ ID No. 6.

10. The polypeptide as claimed in claim 1, characterised in that the

polypeptide contains one or more sequences according to SEQ ID No. 7.

11. The polypeptide as claimed in claim 1, characterised in that the polypeptide contains a variant of the SEQ ID No. 1.

12. The polypeptide as claimed in claim 1, characterised in that the polypeptide is fused to at least one peptide or protein.

13. The polypeptide as claimed in claim 12, characterised in that the protein or peptide is selected from the group consisting of an enzyme, a growth factor, a hormone, a cytokine, a chemokine, a viral coat protein, and an antibody.

14. The polypeptide as claimed in either of claims 12 or 13, characterised in that the protein or peptide is capable of binding specifically to a receptor.

15. The polypeptide as claimed in claim 1, characterised in that the polypeptide is coupled to at least one component.

16. The polypeptide as claimed in claim 15, characterised in that the component is selected from the group consisting of a peptide, a protein, an enzyme, a growth factor, a hormone, a cytokine, a chemokine, a viral coat protein, a carbohydrate, an antibody, a lipid, an isotope, a liposome, a virus, a virus-like particle, a nucleic acid, and/or a cell.

17. The polypeptide as claimed in claim 15 or 16, characterised in that the component is capable of binding specifically to a receptor.

18. The polypeptide as claimed in claim 17, characterised in that the liposome contains at least one antisense RNA, at least one nucleic acid coding for an active agent or at least one active substance.

19. The polypeptide as claimed in claim 18, characterised in that the active substance is a chemotherapeutic agent

20. A nucleic acid, characterised in that said nucleic acid codes for a polypeptide according to claim 1.

21. A vector, characterised in that said vector contains at least one nucleic acid according to claim 20.

22. A cell, characterised in that said cell contains at least one nucleic acid according to claim 20 and/or at least one vector according to claim 21.

23. A method of manufacturing a polypeptide according to claim 1, characterised in that at least one nucleic acid according to claim 20 is expressed in a cell.

24. The method as claimed in claim 23, characterised in that, in a further step, at least one component is coupled to the polypeptide.

25. The use of at least one polypeptide as claimed in claim 1 to detect endoglin and/or endoglin-expressing cells or cell components in vitro and/or in vivo.

26. The use as claimed in claim 25, characterised in that detection is carried out with an ELISA, a RIA, immunofluorescence, immunoprecipitation or immunoscintillation.

27. The use of at least one polypeptide as claimed in claim 1 for

binding to endoglin-expressing cells, characterised in that the binding of the polypeptide has a cytotoxic effect on the endoglin-expressing cell.

28. The use of at least one polypeptide as claimed in claim 1, for the infection, transduction or transfection of endoglin-expressing cells.

29. The use of at least one polypeptide as claimed in claim 1, of at least one nucleic acid as claimed in claim 20 and/or of at least one vector as claimed in claim 21 for the production of a drug for the diagnosis and/or treatment of a disease which is characterised by the hyperproliferation of endoglin-expressing cells.

30. The use as claimed in claim 29, characterised in that the disease is a tumour disease.

31. A pharmaceutical or diagnostic agent containing at least one polypeptide as claimed in claim 1, at least one nucleic acid as claimed in 20, and/or at least one vector as claimed in claim 21 and optionally suitable excipients and additives.

L19 ANSWER 7 OF 11 USPATFULL on STN
2003:271073 Antibody targeting compounds.
Barbas, Carlos F., Solana Beach, CA, UNITED STATES
Rader, Christoph, San Diego, CA, UNITED STATES
Sinha, Subhash C., San Diego, CA, UNITED STATES
Lerner, Richard A., La Jolla, CA, UNITED STATES
The Scripps Research Institute, La Jolla, CA, UNITED STATES, US (U.S. corporation)
US 2003190676 A1 20031009
APPLICATION: US 2003-420373 A1 20030421 (10)
PRIORITY: US 2002-412455P 20020919 (60)
US 2001-344614P 20011022 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An integrin targeting compound comprising, an RGD peptidomimetic-antibody complex wherein: a) said RGD peptidomimetic binds to one or both of $\alpha v\beta 3$ and $\alpha v\beta 5$; b) said antibody does not bind to $\alpha v\beta 3$ or $\alpha v\beta 5$; c) said complex results from an association between the RGD peptidomimetic and the combining site of the antibody; and d) said integrin targeting compound competes for binding between one or both of $\alpha v\beta 3$ and $\alpha v\beta 5$ and a protein selected from the group consisting of vitronectin, and fibrinogen.

2. The composition of claim 1 wherein said association between the RGD peptidomimetic and the combining site of the antibody is covalent.

3. The composition of claim 2 wherein said covalent association is achieved by a **linker** that extends from the targeting agent to the protein.

4. The integrin targeting compound of claim 1 wherein said antibody is a catalytic antibody.

5. The integrin targeting compound of claim 4 wherein said catalytic antibody is selected from the group consisting of an aldolase antibody, a beta lactamase antibody and an esterase antibody or an amidase antibody.

6. The integrin targeting compound of claim 2 wherein said RGD peptidomimetic is linked to the combining site of said antibody via a **complementarity determining region**.

7. The integrin targeting compound of claim 2 wherein said RGD peptidomimetic is linked to the combining site of said antibody via a variable **framework region**.

8. The integrin targeting compound of claim 1 wherein said antibody is full length.

9. The integrin targeting compound of claim 1 wherein said antibody is a fragment of a full length antibody.

10. The integrin targeting compound of claim 9 wherein said fragment of a full length antibody is Fab, Fab' F(ab')2, Fv or sFv.

11. The integrin targeting compound of claim 1 wherein said antibody is a human antibody, humanized antibody or chimeric human antibody.

12. The integrin targeting compound of claim 2 wherein RGD peptidomimetic is linked covalently to a linear or branched **linker** which is linked covalently to the antibody combining site.

13. The integrin targeting compound of claim 12 wherein said **linker** comprises a linear stretch of between 5-100 atoms selected from the group consisting of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof.

14. The integrin targeting compound of claim 12 wherein said **linker** comprises one or more groups selected from alkyl, alkenyl, alkynyl, oxoalkyl, oxoalkenyl, oxoalkynyl, aminoalkyl, aminoalkenyl, aminoalkynyl, sulfoalkyl, sulfoalkenyl, sulfoalkynyl group, phosphoalkyl, phosphoalkenyl, and phosphoalkynyl.

15. The targeting agent-**linker** of claim 12 wherein said **linker** comprises a repeating ether unit of between 2-100 units.

16. The targeting agent-**linker** of claim 12 wherein said **linker** comprises a heterocarbyl structure of the formula ##STR6## wherein R2 to R4 is C, H, N, O, P, S, Si, halogen (F, Cl, Br, I) or a salt thereof; n is 1-100; and m is 1-100.

17. The integrin targeting compound of claim 12 wherein said **linker** comprises one or more ring structures.

18. The integrin targeting compound of claim 17 wherein said one or more ring structures includes one or more six membered rings of the formula ##STR7## wherein A, Z, Y, X or W are independently C or N.

19. The integrin targeting compound of claim 18 wherein said one or more ring structures includes one or more five membered rings of the formula ##STR8## wherein A, Z, Y or X are independently C, O, N or S.

20. The integrin targeting compound of claim 1 further comprising a biological agent.

21. The integrin targeting compound of claim 2 wherein said covalent linkage is nonreversible.

22. The integrin targeting compound of claim 2 wherein said covalent

linkage is reversible.

23. The integrin targeting compound of claim 2 wherein said covalent linkage is labile.

24. The integrin targeting compound of claim 2 wherein said labile linkage is a pH sensitive linkage, is a substrate for an enzyme or is susceptible to degradation by radiation.

25. The integrin targeting compound of claim 12 wherein said covalent linkage between said RGD peptidomimetic and said **linker** or between said **linker** and said antibody or both is nonreversible.

26. The integrin targeting compound of claim 12 wherein said covalent linkage between said RGD peptidomimetic and said **linker** or between said **linker** and said antibody or both is reversible.

27. The integrin targeting compound of claim 12 wherein said covalent linkage between said RGD peptidomimetic and said **linker** or between said **linker** and said antibody or both is labile.

28. The integrin targeting compound of claim 27 wherein said labile linkage is a pH sensitive linkage, is a substrate for an enzyme or is susceptible to degradation by radiation.

29. An agent-**linker**-antigen compound for noncovalently linking to the combining site of an antibody, wherein: a) said agent is an RGD peptidomimetic that binds to one or both of $\alpha v\beta 3$ and $\alpha v\beta 5$; b) said antigen comprises at least one antigenic determinant recognized by the antibody combining site; c) said said **linker** is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof. d) said agent-**linker**-antigen compound competes for binding between one or both of $\alpha v\beta 3$ and $\alpha v\beta 5$ and a protein selected from the group consisting of vitronectin and fibrinogen.

30. The agent-**linker**-antigen compound of claim 29 wherein said **linker** comprises one or more groups selected from alkyl, alkenyl, alkynyl, oxoalkyl, oxoalkenyl, oxoalkynyl, aminoalkyl, aminoalkenyl, aminoalkynyl, sulfoalkyl, sulfoalkenyl, sulfoalkynyl group, phosphoalkyl, phosphoalkenyl, and phosphoalkynyl.

31. The agent-**linker**-antigen compound of claim 29 wherein said **linker** comprises one or more mono or fused homo or hetero saturated or unsaturated 5 to 7 membered carbocyclic ring.

32. The agent-**linker**-antigen compound of claim 29 wherein said **linker** is branched.

33. The agent-**linker**-antigen compound of claim 29 wherein at least two of said of said agents are linked to a different branch of said branched **linker**.

34. An agent-**linker** compound for covalently linking to a combining site of an antibody, wherein: a) said agent is an RGD peptidomimetic that binds to one or both of $\alpha v\beta 3$ and $\alpha v\beta 5$; b) said **linker** is of the formula X--Y--Z wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof, Y if present is a single or fused 5 or 6 membered homo- or heterocarbocylic saturated or unsaturated ring; and Z is a ketone, diketone, beta

lactam, active ester, haloketone, lactone, anhydride, epoxide, aldehyde, maleimide disulfide, or aryl halide; wherein Z is a reactive group for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody, said targeting agents or biological agents linked to X or Y if present or both X and Y if Y is present; and c) said agent-**linker** compound competes for binding between one or both of αvβ3 and αvβ5 and a protein
selected from the group consisting of vitronectin, and fibrinogen.

35. The agent-**linker** of claim 34 wherein said agents are linked in such a way as to retain the ability to bind a target or exhibit a biological activity.

36. The agent-**linker** of claim 34 wherein X comprises a linear stretch of between 5-200 atoms.

37. The targeting agent-**linker** of claim 34 wherein X is a heterocarbyl structure of the formula ##STR9## wherein R_2 to R_4 is C, H, N, O, P, S, Si, halogen (F, Cl, Br, I) or a salt thereof; n is 1-100; and m is 1-100.

38. The agent-**linker** of claim 34 wherein Y is a six membered ring of the formula ##STR10## wherein A, Z, Y, X or W are independently C or N.

39. The agent-**linker** of claim 34 wherein Y is a five membered ring of the formula ##STR11## wherein A, Z, Y or X are independently C, O, N or S.

40. The agent-**linker** of claim 34 wherein said **linker** is branched by addition of one or more connecting chains, said **linker** comprises more than one recognition group, said **linker** comprises more than one reactive group, or combinations thereof.

41. The agent-**linker** of claim 34 wherein said **linker** has the structure below wherein n is from 1-100. ##STR12##

42. An integrin targeting agent comprising the agent-**linker** of claim 34 covalently linked to the combining site of an antibody.

43. An agent-**linker** compound for covalently linking to a combining site of an antibody, wherein: a) said agent is an RGD peptidomimetic that binds to one or both of αvβ3 and
αvβ5; b) said **linker** of the formula X--Y--Z
wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof, and comprising a repeating ether unit of between 0-100 units; Y is a single or fused 5 or 6 membered homo- or heterocarbocylic saturated or unsaturated ring located within 1-20 atoms of Z; and Z is a reactive group for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody; and c) said agent-**linker** compound competes for binding between one or both of αvβ3 and αvβ5 and a protein
selected from the group consisting of vitronectin and fibrinogen.

44. The agent-**linker** of claim 43 wherein said agents are linked in such a way as to retain the ability to bind a target or exhibit a biological activity.

45. The agent-**linker** of claim 43 wherein Z is selected from the group consisting of a ketone, diketone, beta lactam, active ester, haloketone, lactone, anhydride, epoxide, aldehyde, maleimide, disulfide, and aryl

halide.

46. The agent-**linker** of claim 43 wherein X comprises a linear stretch of between 10-200 atoms.

47. The agent-**linker** of claim 126 wherein X is a hetercarbyl of the formula ##STR13## wherein R2 to R4 is C, H, N, O, P, S, Si, halogen (F, Cl, Br, I) or a salt thereof n is 1-100 and m is 1-100

48. The targeting agent-**linker** of claim 43 wherein Y is a six membered ring of the formula ##STR14## wherein A, Z, Y, X or W are independently C or N.

49. The targeting agent-**linker** of claim 43 wherein Y is a five membered ring of the formula ##STR15## wherein A, Z, Y or X are independently C, O, N or S.

50. The targeting agent-**linker** of claim 43 wherein said **linker** comprises more than one connecting chain, more than one recognition group or more than one reactive group, or combinations thereof.

51. An integrin targeting agent comprising the agent-**linker** of claim 34 covalently linked to the combining site of an antibody.

52. An integrin targeting agent comprising the agent-**linker** of claim 43 covalently linked to the combining site of an antibody.

53. A CCR5 targeting compound comprising, a CCR5 chemokine peptidomimetic-antibody complex wherein: a) said CCR5 chemokine peptidomimetic binds to CCR5; b) said antibody does not bind to CCR5 c) said complex results from an association between the CCR5 chemokine peptidomimetic and the combining site of the antibody; and d) said CCR5 targeting compound competes for binding between CCR5 and a β-chemokine.

54. An agent-**linker** compound for covalently linking to a combining site of an antibody, wherein: a) said agent is a CCR5 peptidomimetic that binds to CCR5; b) said **linker** is of the formula X--Y--Z wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof, Y if present is a single or fused 5 or 6 membered homo- or heterocarbocylic saturated or unsaturated ring; and Z is a ketone, diketone, beta lactam, active ester, haloketone, lactone, anhydride, epoxide, aldehyde, maleimide disulfide, or aryl halide; wherein Z is a reactive group for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody, said targeting agents or biological agents linked to X or Y if present or both X and Y if Y is present; and c) said agent-**linker** compound competes for binding between CCR5 and a β-chemokine.

55. An agent-**linker** compound for covalently linking to a combining site of an antibody, wherein: a) said agent is a CCR5 peptidomimetic that binds to CCR5; b) said **linker** of the formula X--Y--Z wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof, and comprising a repeating ether unit of between 0-100 units; Y is a single or fused 5 or 6 membered homo- or heterocarbocylic saturated or unsaturated ring located within 1-20 atoms of Z; and Z is a reactive group for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody; and c) said agent-**linker** compound competes for binding between CCR5 and β-chemokine.

56. A LHRH targeting compound comprising, an LHRH peptide-antibody complex wherein: a) said LHRH peptide binds to the LHRH receptor; b) said antibody does not bind to the LHRH receptor, c) said complex results from an association between the LHRH peptide and the combining site of the antibody; and d) said LHRH targeting compound competes for binding between LHRH and the LHRH receptor.

57. An agent-**linker** compound for covalently linking to a combining site of an antibody, wherein: a) said agent is an LRHR peptide that binds to the LHRH receptor; b) said **linker** is of the formula X--Y--Z wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof, Y if present is a single or fused 5 or 6 membered homo- or heterocarbocylic saturated or unsaturated ring; and Z is a ketone, diketone, beta lactam, active ester, haloketone, lactone, anhydride, epoxide, aldehyde, maleimide disulfide, or aryl halide; wherein Z is a reactive group for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody, said targeting agents or biological agents linked to X or Y if present or both X and Y if Y is present; and c) said agent-**linker** compound competes for binding between LHRH and the LHRH receptor.

58. An agent-**linker** compound for covalently linking to a combining site of an antibody, wherein: a) said agent is an LHRH peptide that binds to the LHRH receptor; b) said **linker** of the formula X--Y--Z wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof, and comprising a repeating ether unit of between 0-100 units; Y is a single or fused 5 or 6 membered homo- or heterocarbocylic saturated or unsaturated ring located within 1-20 atoms of Z; and Z is a reactive group for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody; and c) said agent-**linker** compound competes for binding between LHRH and the LHRH receptor.

59. An HIV-1 membrane fusion inhibiting compound-antibody complex wherein: a) said HIV-1 membrane fusion inhibiting compound inhibits fusion of HIV-1 to a target cell; b) said antibody does not inhibit fusion of HIV-1 to a target cell; and c) said complex results from an association between the HIV-1 membrane fusion inhibiting compound and the combining site of the antibody.

60. The HIV-1 membrane fusion inhibiting compound-antibody complex of claim 59 wherein said HIV-1 membrane fusion inhibiting compound comprises a peptide or peptidomimetic of an HIV-1 envelope protein.

61. The HIV-1 membrane fusion inhibiting compound-antibody complex of claim 59 wherein said HIV-1 membrane fusion inhibiting compound comprises a small molecular weight organic molecule that binds to an HIV-1 envelope protein.

62. An agent-**linker** compound for covalently linking to a combining site of an antibody, wherein: a) said agent is an HIV-1 membrane fusion inhibiting compound; b) said **linker** is of the formula X--Y--Z wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof, Y if present is a single or fused 5 or 6 membered homo- or heterocarbocylic saturated or unsaturated ring; and Z is a ketone, diketone, beta lactam, active ester, haloketone, lactone, anhydride, epoxide, aldehyde, maleimide disulfide, or aryl halide; wherein Z is a reactive group for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody, said targeting agents or biological

agents linked to X or Y if present or both X and Y if Y is present; and c) said agent-**linker** compound inhibits HIV-1 fusion to a cell membrane.

63. An agent-**linker** compound for covalently linking to a combining site of an antibody, wherein: a) said agent is HIV-1 membrane fusion inhibiting compound; b) said **linker** of the formula X--Y--Z wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof, and comprising a repeating ether unit of between 0-100 units; Y is a single or fused 5 or 6 membered homo- or heterocarbocylic saturated or unsaturated ring located within 1-20 atoms of Z; and Z is a reactive group for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody; and c) said agent-**linker** compound inhibits HIV-1 fusion to a cell membrane.

64. A thrombopoietin (TPO) receptor targeting compound comprising, a TPO peptide or peptidomimetic-antibody complex wherein: a) said peptide or peptidomimetic binds to the TPO receptor; b) said antibody does not bind to the TPO receptor; c) said complex results from an association between the peptide or peptidomimetic and the combining site of the antibody; and d) said TPO receptor targeting compound competes for binding between TPO and the TPO receptor.

65. An agent-**linker** compound for covalently linking to a combining site of an antibody, wherein: a) said agent is a thrombopoietin (TPO) receptor peptide or peptidomimetic that binds to the TPO receptor; b) said **linker** is of the formula X--Y--Z wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, ora salt thereof, Y if present is a single or fused 5 or 6 membered homo- or heterocarbocylic saturated or unsaturated ring; and Z is a ketone, diketone, beta lactam, active ester, haloketone, lactone, anhydride, epoxide, aldehyde, maleimide disulfide, or aryl halide; wherein Z is a reactive group for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody, said targeting agents or biological agents linked to X or Y if present or both X and Y if Y is present; and c) said agent-**linker** compound competes for binding between TPO and the TPO receptor.

66. An agent-**linker** compound for covalently linking to a combining site of an antibody, wherein: a) said agent is a thrombopoietin (TPO) receptor peptide or peptidomimetic that binds to the TPO receptor; b) said **linker** of the formula X--Y--Z wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof, and comprising a repeating ether unit of between 0-100 units; Y is a single or fused 5 or 6 membered home or heterocarbocylic saturated or unsaturated ring located within 1-20 atoms of Z; and Z is a reactive group for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody; and c) said agent-**linker** compound competes for binding between TPO and the TPO receptor.

L19 ANSWER 8 OF 11 USPATFULL on STN
2003:251135 Antibody targeting compounds.
Barbas, Carlos F., Solana Beach, CA, UNITED STATES
Rader, Christoph, San Diego, CA, UNITED STATES
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The Scripps Research Institute (U.S. corporation)
US 2003175921 A1 20030918
APPLICATION: US 2002-278364 A1 20021022 (10)

PRIORITY: US 2001-344614P 20011022 (60)
US 2002-412455P 20020919 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. An antibody targeting compound comprising one or more targeting agents or one or more biological agents or comprising one or more targeting agents and one or more biological agents, said agents covalently linked to the combining site of an antibody.

2. The antibody targeting compound of claim 1 wherein said agents are linked in such a way as to retain the ability to bind a target or exhibit a biological activity.

3. The antibody targeting compound of claim 1 wherein said agents is not an antibody.

4. The antibody targeting compound of claim 1 wherein said the antigen binding specificity of the antibody before covalent linkage is not substantially modified following covalent linkage.

5. The antibody targeting compound of claim 1 wherein said antigen binding specificity of the antibody before covalent linkage is substantially modified following covalent linkage.

6. The antibody targeting compound of claim 1 wherein said agents are specific for a non-immunoglobulin molecule.

7. The antibody targeting compound of claim 1 wherein said agents are specific for an immunoglobulin molecule and bind the immunoglobulin outside of its combining site.

8. The antibody targeting compound of claim 1 wherein said antibody is a catalytic antibody.

9. The antibody targeting compound of claim 8 wherein said catalytic antibody is selected from the group consisting of an aldolase antibody, a beta lactamase antibody and an esterase antibody or an amidase antibody.

10. The antibody targeting compound of claim 1 wherein said agents are linked to the combining site of said antibody via a **complementarity determining region**.

11. The antibody targeting compound of claim 1 wherein said agents are linked to the combining site of said antibody via a variable **framework region**.

12. The antibody targeting compound of claim 1 wherein said antibody is full length.

13. The antibody targeting compound of claim 1 wherein said antibody is a fragment of a full length antibody.

14. The antibody targeting compound of claim 13 wherein said fragment of a full length antibody is Fab, Fab' F(ab')2, Fv or sFv.

15. The antibody targeting compound of claim 1 wherein said antibody is a human antibody, humanized antibody or chimeric human antibody.

16. The antibody targeting compound of claim 1 wherein said agents are linked covalently to a linear or branched **linker** which is linked

covalently to the antibody combining site.

17. The antibody targeting compound of claim 16 wherein said **linker** comprises a linear stretch of between 5-100 atoms selected from the group consisting of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof.

18. The antibody targeting compound of claim 16 wherein said **linker** comprises one or more groups selected from alkyl, alkenyl, alkynyl, oxoalkyl, oxoalkenyl, oxoalkynyl, aminoalkyl, aminoalkenyl, aminoalkynyl, sulfoalkyl, sulfoalkenyl, sulfoalkynyl group, phosphoalkyl, phosphoalkenyl, and phosphoalkynyl.

19. The targeting agent-**linker** of claim 16 wherein said **linker** comprises a repeating ether unit of between 2-100 units.

20. The targeting agent-**linker** of claim 16 wherein said **linker** comprises a heterocarbyl structure of the formula ##STR6## wherein R2 to R4 is C, H, N, O, P, S, Si, halogen (F, Cl, Br, I) or a salt thereof; n is 1-100; and m is 1-100.

21. The antibody targeting compound of claim 16 wherein said **linker** comprises one or more ring structures.

22. The antibody targeting compound of claim 21 wherein said one or more ring structures includes one or more six membered rings of the formula ##STR7## wherein A, Z, Y, X or W are independently C or N.

23. The antibody targeting compound of claim 20 wherein said one or more ring structures includes one or more five membered rings of the formula ##STR8## wherein A, Z, Y or X are independently C, O, N or S.

24. The antibody targeting compound of claim 1 wherein two or more targeting agents or two or more biological agents are linked to the combining site of the antibody.

25. The antibody targeting compound of claim 24 wherein said two or more targeting agents or two or more biological agents are the same.

26. The antibody targeting compound of claim 24 wherein said two or more targeting agents or two or more biological agents are different.

27. The antibody targeting compound of claim 1 wherein said antibody targeting compound comprises two targeting agents or two biological agents, said antibody has two combining sites, and each of said combining sites is linked to a targeting agent or a biological agent.

28. The antibody targeting compound of claim 1 wherein at least one of said one or more biological agent is a therapeutic drug.

29. The antibody targeting compound of claim 1 wherein said therapeutic drug is a prodrug.

30. The antibody targeting compound of claim 1 wherein at least one of said targeting agents or biological agents is specific for a biomolecule.

31. The antibody targeting compound of claim 30 wherein said biomolecule is a cell surface expressed or particle surface expressed ligand or receptor.

32. The antibody targeting compound of claim 31 wherein said cell

surface expressed ligand or receptor is an integrin, a folate receptor, a cytokine receptor, an interleukin receptor, a viral protein or an enzyme.

33. The antibody targeting compound of claim 31 wherein said biomolecule is a fluid phase biomolecule.

34. The antibody targeting compound of claim 31 wherein said biomolecule is an extracellular matrix biomolecule.

35. The antibody targeting compound of claim 1 wherein said covalent linkage is nonreversible.

36. The antibody targeting compound of claim 1 wherein said covalent linkage is reversible.

37. The antibody targeting compound of claim 1 wherein said covalent linkage is labile.

38. The antibody targeting compound of claim 1 wherein said labile linkage is a pH sensitive linkage, is a substrate for an enzyme or is susceptible to degradation by radiation.

39. The antibody targeting compound of claim 16 wherein said covalent linkage between said agent and said **linker** or between said **linker** and said antibody or both is nonreversible.

40. The antibody targeting compound of claim 16 wherein said covalent linkage between said agent and said **linker** or between said **linker** and said antibody or both is reversible.

41. The antibody targeting compound of claim 16 wherein said covalent linkage between said agent and said **linker** or between said **linker** and said antibody or both is labile.

42. The antibody targeting compound of claim 16 wherein said labile linkage is a pH sensitive linkage, is a substrate for an enzyme or is susceptible to degradation by radiation.

43. A method of producing an antibody targeting compound comprising one or more targeting agents or one or more biological agents or comprising one or more targeting agents and one or more biological agents, said method comprising covalently linking said agents to the combining site of an antibody

44. The method of claim 43 wherein said agents are linked in such a way as to retain the ability to bind a target or exhibit a biological activity.

45. The method of claim 43 wherein said linking is achieved using a linear or branched **linker**.

46. The method of claim 45 wherein said linking is achieved by preparing an agent **linker** compound comprising a targeting agent or a biological agent or both and a **linker** comprising a reactive group for reaction with the combining site of an antibody, and linking said reactive group of said **linker** of said agent-**linker** compound covalently to the combining site of the antibody.

47. The method of claim 45 wherein said linking is achieved by preparing an antibody-**linker** compound comprising an antibody and a **linker** comprising a reactive group for reaction said one or more targeting

agents or biological agents, and linking the reactive group of the antibody-**linker** compound to said one or more targeting agents or biological agents.

48. The method of claim 45 wherein said linking is achieved by: (a) preparing an agent **linker** compound comprising a targeting agent or a biological agent or both and a **linker** comprising a reactive group; and (b) preparing an antibody-**linker** compound comprising an antibody and a **linker** comprising a chemical group suitable for reaction with the reactive group of step (a); or (c) preparing an antibody-**linker** compound comprising an antibody and a **linker** comprising a reactive group; and (d) preparing an agent **linker** compound comprising a targeting agent or a biological agent or both and a **linker** comprising a chemical group reactive with said reactive group of step (c); and (e) linking the **linker** of said antibody-**linker** compound to the **linker** of the targeting agent-**linker** compound or biological agent-**linker** compound through said reactive and susceptible groups.

49. The method of claim 43 wherein said agents are not an antibody.

50. The method of claim 43 wherein said the antigen binding specificity of the antibody before covalent linkage is not substantially modified following covalent linkage.

51. The method of claim 43 wherein said antigen binding specificity of the antibody before covalent linkage is substantially modified following covalent linkage.

52. The method of claim 43 wherein said agents are specific for a non-immunoglobulin molecule.

53. The method of claim 43 wherein said agents are specific for an immunoglobulin molecule and bind the immunoglobulin outside of its combining site.

54. The method of claim 43 wherein said antibody is a catalytic antibody.

55. The method of claim 54 wherein said catalytic antibody is selected from the group consisting of an aldolase antibody, a beta lactamase antibody and an esterase antibody or an amidase antibody.

56. The method of claim 43 wherein said agents are linked to the combining site of said antibody via a **complementarity determining region**.

57. The method of claim 43 wherein said agents are linked to the combining site of said antibody via a variable **framework region**.

58. The method of claim 43 wherein said antibody is full length.

59. The method of claim 43 wherein said antibody is a fragment of a full length antibody.

60. The method of claim 59 wherein said fragment of a full length antibody is Fab, Fab' F(ab')2, Fv or sFv.

61. The method of claim 43 wherein said antibody is a human antibody, humanized antibody or chimeric human antibody.

62. The method of claim 45 wherein said **linker** comprises a linear stretch of between 5-100 atoms selected from the group consisting of C,

H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof.

63. The method of claim 45 wherein said **linker** comprises one or more groups selected from alkyl, alkenyl, alkynyl, oxoalkyl, oxoalkenyl, oxoalkynyl, aminoalkyl, aminoalkenyl, aminoalkynyl, sulfoalkyl, sulfoalkenyl, sulfoalkynyl group, phosphoalkyl, phosphoalkenyl, and phosphoalkynyl.

64. The method of claim 45 wherein said **linker** comprises a repeating ether unit of between 2-100 units.

65. The method of claim 45 wherein said **linker** is of the formula X-Y-Z wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof; Y if present is a single or fused 5 or 6 membered homo- or heterocarbocylic saturated or unsaturated ring; and Z is the reactive group.

66. The method of claim 65 wherein X is a heterocarbyl structure of the formula ##STR9## wherein R2 to R4 is C, H, N, O, P, S, Si, halogen (F, Cl, Br, I) or a salt thereof; n is 1-100; and m is 1-100.

67. The method of claim 45 wherein said **linker** comprises one or more ring structures.

68. The method of claim 67 wherein said one or more ring structures includes one or more six membered rings of the formula ##STR10## wherein A, Z, Y, X or W are independently C or N.

69. The method of claim 67 wherein said one or more ring structures includes one or more five membered rings of the formula ##STR11## wherein A, Z, Y or X are independently C, O, N or S.

70. The method of claim 45 wherein said **linker** has the structure below wherein n is from 1-100. ##STR12##

71. The method of claim 43 wherein two or more targeting agents or two or more biological agents are linked to the combining site of the antibody.

72. The method of claim 71 wherein said two or more targeting agents or two or more biological agents are the same.

73. The method of claim 71 wherein said two or more targeting agents or two or more biological agents are different.

74. The method of claim 43 wherein at least one of said one or more biological agent is a therapeutic drug.

75. The method of claim 74 wherein said therapeutic drug is a prodrug.

76. The method of claim 45 wherein said **linker** comprises more than one connecting chain, more than one recognition group or more than one reactive group, or combinations thereof.

77. The method of claim 43 wherein at least one of said targeting agents or biological agents is specific for a biomolecule.

78. The method of claim 77 wherein said biomolecule is a cell surface expressed or particle surface expressed ligand or receptor.

79. The method of claim 78 wherein said cell surface expressed ligand or receptor is an integrin, a folate receptor, a cytokine receptor, an

interleukin receptor, a viral protein or an enzyme.

80. The method of claim 77 wherein said biomolecule is a fluid phase biomolecule.

81. The method of claim 77 wherein said biomolecule is an extracellular matrix biomolecule.

82. The method of claim 43 wherein said covalent linkage is nonreversible.

83. The method of claim 43 wherein said covalent linkage is reversible.

84. The method of claim 43 wherein said covalent linkage is labile.

85. The method of claim 84 wherein said labile linkage is a pH sensitive linkage, is a substrate for an enzyme or is susceptible to degradation by radiation.

86. The method of claim 45 wherein said covalent linkage between said agent and said **linker** or between said **linker** and said antibody or both is nonreversible.

87. The method of claim 45 wherein said covalent linkage between said agent and said **linker** or between said **linker** and said antibody or both is reversible.

88. The method of claim 45 wherein said covalent linkage between said agent and said **linker** or between said **linker** and said antibody or both is labile.

89. The method of claim 88 wherein said labile linkage is a pH sensitive linkage, is a substrate for an enzyme or is susceptible to degradation by radiation.

90. An antibody targeting compound produced by the method of claim 43.

91. A method of modifying an antibody which exhibits low or nondetectable binding affinity for a particular target molecule so that the antibody has increased binding specificity for the particular target molecule, said method comprising covalently linking one or more targeting agents or biological agents specific for the particular target molecule to the combining site of the antibody to generate an antibody targeting compound, wherein said agents are linked in such a way as to retain the ability to bind the particular target molecule.

92. The method of claim 91 wherein said antibody prior to covalent linking exhibits an affinity for said particular target molecule of less than about 1x10-5 moles/liter.

93. The method of claim 91 wherein said antibody after covalent linking exhibits an affinity for said particular target molecule of greater than about 1x10-6 moles/liter.

94. The method of claim 91 wherein said antibody is a catalytic antibody.

95. The method of claim 91 wherein said linking is achieved using a linear or branched **linker**.

96. The method of claim 91 wherein said linking is achieved by preparing a targeting agent-**linker** compound comprising one or more targeting

agents and a **linker** comprising a reactive group for reaction with the combining site of the antibody, and linking said reactive group of said **linker** of said targeting agent-**linker** compound covalently to the combining site of the antibody.

97. The method of claim 91 wherein said linking is achieved by preparing an antibody-**linker** compound comprising an antibody and a **linker** comprising a reactive group for reaction said one or more targeting agents, and linking the reactive group of the antibody-**linker** compound to said one or more targeting agents.

98. The method of claim 91 wherein said linking is achieved by: (a) preparing a targeting agent **linker** compound comprising a targeting agent and a **linker** comprising a reactive group; and (b) preparing an antibody-**linker** compound comprising an antibody and a **linker** comprising a chemical group suitable for reaction with the reactive group of step (a); or (c) preparing an antibody-**linker** compound comprising an antibody and a **linker** comprising a reactive group; and (d) preparing a targeting agent-**linker** compound comprising a targeting agent and a **linker** comprising a chemical group reactive with said reactive group of step (c); and (e) linking the **linker** of said antibody-**linker** compound to the **linker** of the targeting agent-**linker** compound through said reactive and susceptible groups.

99. The method of claim 91 wherein said one or more targeting agents is not an antibody.

100. An antibody targeting compound produced by the method of claim 91.

101. A method of altering at least one biological characteristic of a targeting agent or biological agent, said method comprising covalently linking the targeting agent or biological agent to the combining site of an antibody, wherein said covalent linking alters at least one biological characteristic of the targeting agent or biological agent.

102. The method of claim 101 wherein said antibody is a catalytic antibody.

103. The method of claim 101 wherein said linking is achieved using a linear or branched **linker**.

104. The method of claim 103 wherein said linking is achieved by preparing an agent **linker** compound comprising a targeting agent or a biological agent or both and a **linker** comprising a reactive group for reaction with the combining site of an antibody, and linking said reactive group of said **linker** of said agent-**linker** compound covalently to the combining site of the antibody.

105. The method of claim 103 wherein said linking is achieved by preparing an antibody-**linker** compound comprising an antibody and a **linker** comprising a reactive group for reaction said one or more targeting agents or biological agents, and linking the reactive group of the antibody-**linker** compound to said one or more targeting agents or biological agents.

106. The method of claim 103 wherein said linking is achieved by: (a) preparing an agent **linker** compound comprising a targeting agent or a biological agent or both and a **linker** comprising a reactive group; and (b) preparing an antibody-**linker** compound comprising an antibody and a **linker** comprising a chemical group suitable for reaction with the reactive group of step (a); or (c) preparing an antibody-**linker** compound comprising an antibody and a **linker** comprising a reactive

group; and (d) preparing an agent **linker** compound comprising a targeting agent or a biological agent or both and a **linker** comprising a chemical group reactive with said reactive group of step (c); and (e) linking the **linker** of said antibody-**linker** compound to the **linker** of the targeting agent-**linker** compound or biological agent-**linker** compound through said reactive and susceptible groups.

107. The method of claim 101 wherein said at least one altered characteristic is pharmocokinetics, pharmacodynamics, immunogenicity binding affinity, susceptibility to degradation, solubility, lipophilicity, hydrophilicity, hydrophobicity, stability, and rigidity.

108. An antibody targeting compound produced by the method of claim 101.

109. An agent-**linker**-antigen compound for noncovalently linking to the combining site of an antibody, said agent-**linker**-antigen compound comprising two or more targeting agents which are not an antibody or comprising two or more biological agents or comprising at least two agents wherein at least one is a targeting agent and another is a biological agent, said agent-**linker** compound covalently linked via a **linker** to an antigen recognized by the antibody, wherein said **linker** is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof.

110. The agent-**linker**-antigen of claim 109 wherein said agents are linked in such a way as to retain the ability to bind a target or exhibit a biological activity.

111. The agent-**linker**-antigen compound of claim 109 wherein said **linker** comprises one or more groups selected from alkyl, alkenyl, alkynyl, oxoalkyl, oxoalkenyl, oxoalkynyl, aminoalkyl, aminoalkenyl, aminoalkynyl, sulfoalkyl, sulfoalkenyl, sulfoalkynyl group, phosphoalkyl, phosphoalkenyl, and phosphoalkynyl.

112. The agent-**linker**-antigen compound of claim 109 wherein said **linker** comprises one or more mono or fused homo or hetero saturated or unsaturated 5 to 7 membered carbocyclic ring.

113. The agent-**linker**-antigen compound of claim 109 wherein said **linker** is branched.

114. The agent-**linker**-antigen compound of claim 109 wherein at least two of said of said agents are linked to a different branch of said branched **linker**.

115. An antibody targeting compound comprising the agent-**linker**-antigen of claim 109 associated non-covalently with the combining site of an antibody specific for said antigen.

116. A method of modifying the binding specificity of an antibody comprising contacting said antibody with the agent-**linker**-antigen of claim 109 wherein said antibody is specific for said antigen and said antibody acquires the binding specificity of the targeting agent or biological agent.

117. An agent-**linker** compound for covalently linking to a combining site of an antibody, said agent-**linker** compound comprising one or more targeting agents or one or biological agents or both, said **linker** of the formula ##STR13## wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof, Y if present is a single or fused 5 or 6 membered homo- or heterocarbocylic saturated or unsaturated ring; and Z is a

ketone, diketone, beta lactam, active ester, haloketone, lactone, anhydride, epoxide, aldehyde, maleimide disulfide, or aryl halide; and wherein Z is a reactive group for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody, said targeting agents or biological agents linked to X or Y if present or both X and Y if Y is present.

118. The agent-**linker** of claim 117 wherein said agents are linked in such a way as to retain the ability to bind a target or exhibit a biological activity.

119. The agent-**linker** of claim 117 wherein X comprises a linear stretch of between 5-200 atoms.

120. The targeting agent-**linker** of claim 117 wherein X is a heterocarbyl structure of the formula ##STR14## wherein R2 to R4 is C, H, N, O, P, S, Si, halogen (F, Cl, Br, I) or a salt thereof; n is 1-100; and m is 1-100.

121. The agent-**linker** of claim 117 wherein Y is a six membered ring of the formula ##STR15## wherein A, Z, Y, X or W are independently C or N.

122. The agent-**linker** of claim 117 wherein Y is a five membered ring of the formula ##STR16## wherein A, Z, Y or X are independently C, O, N or S.

123. The agent-**linker** of claim 117 wherein said **linker** is branched by addition of one or more connecting chains, said **linker** comprises more than one recognition group, said **linker** comprises more than one reactive group, or combinations thereof.

124. The agent-**linker** of claim 117 wherein said **linker** has the structure below wherein n is from 1-100. ##STR17##

125. An antibody targeting agent comprising the agent-**linker** of claim 117 covalently linked to the combining site of an antibody.

126. An agent-**linker** compound for covalently linking to a combining site of an antibody, said agent-**linker** compound comprising one or more targeting agents or one or more biological agents or both, said **linker** of the formula ##STR18## wherein X is a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or a salt thereof, and comprising a repeating ether unit of between 0-100 units; Y is a single or fused 5 or 6 membered homo- or heterocarbocylic saturated or unsaturated ring located within 1-20 atoms of Z; and Z is a reactive group for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody.

127. The agent-**linker** of claim 126 wherein said agents are linked in such a way as to retain the ability to bind a target or exhibit a biological activity.

128. The agent-**linker** of claim 126 wherein Z is selected from the group consisting of a ketone, diketone, beta lactam, active ester, haloketone, lactone, anhydride, epoxide, aldehyde, maleimide, disulfide, and aryl halide.

129. The agent-**linker** of claim 126 wherein X comprises a linear stretch of between 10-200 atoms.

130. The agent-**linker** of claim 126 wherein X is a hetercarbyl of the formula ##STR19## wherein R2 to R4 is C, H, N, O, P, S, Si, halogen (F, Cl, Br, I) or a salt thereof n is 1-100 and m is 1-100

131. The targeting agent-**linker** of claim 126 wherein Y is a six membered ring of the formula ##STR20## wherein A, Z, Y, X or W are independently C or N.

132. The targeting agent-**linker** of claim 126 wherein Y is a five membered ring of the formula ##STR21## wherein A, Z, Y or X are independently C, O, N or S.

133. The targeting agent-**linker** of claim 126 wherein said **linker** comprises more than one connecting chain, more than one recognition group or more than one reactive group, or combinations thereof.

134. An antibody targeting agent comprising the agent-**linker** of claim 126 covalently linked to the combining site of an antibody.

135. A method of delivering a biological activity to cells, tissue extracellular matrix biomolecule or a biomolecule in the fluid of an individual, said method comprising administering to the individual the antibody targeting compound of any of claims 1, 90, 120, 108, 115, 125, or 134 wherein said antibody targeting compound is specific for said cells, tissue extracellular matrix biomolecule or fluid biomolecule and wherein said antibody targeting compound comprises a biological activity.

136. A method of treating or preventing a disease or condition in an individual wherein said disease or condition involves cells, tissue or fluid that expresses a target molecule, said method comprising administering to the individual a therapeutically effective amount of the antibody targeting compound of any of claims 1, 90, 120, 108, 115, 125, or 134 wherein said antibody targeting compound is specific for said target molecule and wherein said targeting compound comprises a biological activity effective against the disease or condition.

137. The method of claim 136 wherein said biological agent is a cytokine, a toxin, a drug, a nucleic acid or an isotope.

138. The method of claim 136 wherein said disease or condition is an infection and said target molecule is expressed by a microbial agent or virus.

139. The method of claim 136 wherein said compound is administered in vivo.

140. The method of claim 136 wherein said compound is administered topically.

141. A method of imaging cells or tissue in an individual wherein said cells or tissue expresses a target molecule, said method comprising administering to the individual the antibody targeting of any of claims 1, 90, 120, 108, 115, 125, or 134 linked to a detectable label.

142. A method of reducing the infectivity of microbial cells or viral particles present on a surface, said method comprising contacting said surface with an effective amount of the antibody targeting compound of any of claims 1, 90, 120, 108, 115, 125, or 134 wherein said antibody targeting compound comprises a targeting agent or biological agent specific for a receptor on said microbial cells or virus particles.

143. A method of screening a chemical library for agonists or antagonists of a receptor, comprising covalently linking individual members of the chemical library to the combining site of an antibody and then testing the antibody linked library for binding to the receptor or for inhibition of binding between the receptor and a ligand for the receptor.

144. The method of claim 143 wherein said receptor is expressed by a cell and said binding or inhibition of binding is determined by detecting a cellular signal resulting from said binding or inhibition of binding.

145. In an immunoassay to determine the amount of analyte in a sample, said method comprising: (a) forming, in a medium containing said sample, a complex between the analyte and at least one antibody specific for the analyte; (b) analyzing said medium to detect the amount of said complex; and (c) relating the amount of said complex to the amount of analyte in the sample, the improvement comprising forming the complex with at least one antibody targeting compound specific for the analyte, said specificity provided by an non-antibody targeting agent or biological agent specific for the analyte, said targeting agent or biological covalently linked to the combining site of the antibody.

146. The assay of claim 145 wherein said antibody prior to covalent linking exhibits an affinity for said analyte of less than about 1x10-5 moles/liter.

147. The assay of claim 145 wherein said antibody after covalent linking exhibits an affinity for said analyte of greater than about 1x10-6 moles/liter.

148. The assay of claim 145 wherein said antibody is a catalytic antibody.

149. In a direct or indirect binding assay where the presence of an analyte is determined by using an antibody specific for the analyte, the improvement comprising determining the presence of said analyte using an antibody targeting compound specific for the analyte, said specificity provided by an non-antibody targeting agent or biological agent specific for the analyte, said targeting agent or biological covalently linked to the combining site of the antibody.

150. The assay of claim 149 wherein said antibody prior to covalent linking exhibits an affinity for said analyte of less than about 1x10-5 moles/liter.

151. The assay of claim 149 wherein said antibody after covalent linking exhibits an affinity for said analyte of greater than about 1x10-6 moles/liter.

152. The assay of claim 149 wherein said antibody is a catalytic antibody.

153. A method of delivering a biological activity to cells, tissue extracellular matrix biomolecule or a biomolecule in the fluid of an individual, said method comprising separately administering to the individual the agent-**linker**-antigen compound of claim 109 and an antibody specific for the antigen, wherein said agent-**linker**-antigen compound non-covalently associates with the antibody combining site in vivo and wherein said agent-**linker**-antigen compound is specific for cells, tissue extracellular matrix biomolecule or fluid biomolecule.

154. A method of treating or preventing a disease or condition in an individual wherein said disease or condition involves cells, tissue or fluid that expresses a target molecule, said method comprising administering to the individual a therapeutically effective amount of the individual the agent-**linker**-antigen compound of claim 109 and an antibody specific for the antigen, wherein said agent-**linker**-antigen are administered separately and non-covalently associate in vivo, said agent-**linker**-antigen compound is specific for cells, tissue extracellular matrix biomolecule or fluid biomolecule, and wherein said agent-**linker**-antigen or antibody comprises a biological activity effective against the disease or condition.

155. The method of claim 154 wherein said biological agent is a cytokine, a toxin, a drug, a nucleic acid or an isotope.

156. The method of claim 154 wherein said disease or condition is an infection and said target molecule is expressed by a microbial agent or virus.

157. The method of claim 154 wherein said compound is administered in vivo.

158. The method of claim 154 wherein said compound is administered topically.

159. A method of imaging cells or tissue in an individual wherein said cells or tissue expresses a target molecule, said method comprising separately administering to the individual the agent-**linker**-antigen compound of claim 109 linked to a detectable label and an antibody specific for the antigen, wherein said agent-**linker**-antigen compound non-covalently associates with the antibody combining site in vivo and wherein said agent-**linker**-antigen compound is specific for the target in said cells or tissue.

160. A method of inhibiting or reducing the ability of a cell penetrating targeting agent or biological agent to cross a cell membrane, said method comprising forming an antibody targeting compound by covalently linking the combining site of an antibody that does not itself cross the cell membrane to the targeting agent or biological agent, wherein linkage of said antibody to said targeting agent or biological agent reduces or inhibits the ability of the agent to cross the cell membrane.

161. The method of claim 160 wherein said agents are linked in such a way as to retain the ability to bind a target or exhibit a biological activity.

162. The method of claim 160 wherein said linking is achieved using a linear or branched **linker**.

163. The method of claim 162 wherein said linking is achieved by preparing an agent **linker** compound comprising a targeting agent or a biological agent or both and a **linker** comprising a reactive group for reaction with the combining site of an antibody, and linking said reactive group of said **linker** of said agent-**linker** compound covalently to the combining site of the antibody.

164. The method of claim 162 wherein said linking is achieved by preparing an antibody-**linker** compound comprising an antibody and a **linker** comprising a reactive group for reaction said one or more targeting agents or biological agents, and linking the reactive group of the antibody-**linker** compound to said one or more targeting agents or

biological agents.

165. The method of claim 162 wherein said linking is achieved by: (a) preparing an agent **linker** compound comprising a targeting agent or a biological agent or both and a **linker** comprising a reactive group; and (b) preparing an antibody-**linker** compound comprising an antibody and a **linker** comprising a chemical group susceptible to reaction with the reactive group of step (a); or (c) preparing an antibody-**linker** compound comprising an antibody and a **linker** comprising a reactive group; and (d) preparing an agent **linker** compound comprising a targeting agent or a biological agent or both and a **linker** comprising a chemical group susceptible to reaction with said reactive group of step (c); and (e) linking the linkers of steps (a) and (b) or steps (c) and (d) covalently together through said reactive and susceptible groups to form the antibody targeting compound.

166. The method of claim 162 wherein said agents are not an antibody.

167. A method of mediating intracellular delivery of an intracellularly active drug, said method comprising: (a) preparing an antibody targeting compound wherein said compound comprises one or more targeting agents or one or more biological agents or both covalently linked via a **linker** to the combining site of said antibody, wherein said one or more targeting agents or biological agents bind to a cell receptor and mediate internalization, and wherein said targeting compound also comprises a drug that is active intracellularly; and (b) contacting a cell expressing said receptor with the antibody targeting compound of step (a), wherein said contacting results in internalization of the antibody targeting agent and delivery of said drug intracellularly.

168. The method of claim 167 wherein said intracellularly active drug is a prodrug that becomes active when said drug contacts an intracellular compartment.

169. The method of claim 167 wherein said antibody targeting compound further comprises a trafficking signal to direct the internalized antibody targeting compound to a particular intracellular compartment.

170. The method of claim 167 wherein two or more targeting agents or biological agents or both are covalently linked to the antibody combining site thereby increasing the avidity between said antibody targeting compound and said cell receptor, resulting in increased receptor mediated internalization and increased drug delivery.

171. A method of modifying a physical or biological property of an antibody targeting compound, said method comprising: (a) preparing an antibody targeting compound comprising an antibody to which one or more targeting agents or one or more biological agents have been covalently linked via a **linker** to the combining site of the antibody; (b) modifying one or more chemical characteristics of the **linker**; and (c) determining if a physical or biological property of the antibody targeting compound has been modified.

172. The method of claim 171 wherein said physical or biological property is pharmacokinetics, pharmacodynamics, immunogenicity, binding affinity, susceptibility to degradation, solubility, lipophilicity, hydrophilicity, hydrophobicity, stability, and rigidity.

L19 ANSWER 9 OF 11 USPATFULL on STN
2003:31094 Reshaped human antibody to human medulloblastoma cells.
Ohtomo, Toshihiko, Gotenba-shi, JAPAN

Sato, Koh, Gotenba-shi, JAPAN
Tsuchiya, Masayuki, Gotenba-shi, JAPAN
US 2003023045 A1 20030130
APPLICATION: US 2000-749873 A1 20001229 (9)
PRIORITY: JP 1993-291078 19931119
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. An L chain variable region (V region) of an antibody to human medulloblastoma cells, comprising three **complementarity determining regions** (CDRs) having the amino acid sequences defined below: CDR1: Lys Ala Ser Gln Asn Val Gly Thr Asn Val Ala CDR2: Ser Ala Ser Tyr Arg Tyr Ser CDR3; Gln Gln Tyr Asn Ser Tyr Pro Arg Ala or a portion thereof and four **framework regions** (FRs).

2. An L chain of antibody to human medulloblastoma cells comprising the L chain variable region (V region) of claim I and human L chain constant region (C region).

3. An L chain according to claim 2 wherein the FRs of said L chain V region are derived from a mouse antibody.

4. An L chain according to claim 2 wherein said L chain V region has the amino acid sequence indicated in SEQ ID NO:26.

5. An L chain according to claim 2 wherein the FRs of said L chain V region are derived from a human antibody.

6. An L chain according to claim 2 or 5 wherein the FRs of said L chain V region are derived from a human antibody REI.

7. An L chain according to claim 5 or 6 wherein the amino acid at position 46 in the second FR of said L chain V region is praline.

8. An L chain according to claim 5 or 6 wherein the amino acids at positions 42, 43 and 46 in the second FR of said L chain V region are glutamine, serine and proline, respectively.

9. An L chain according to claim 2 wherein said L chain V region includes either set of four FRs having the following amino acid sequences: (1) FRI: Asp Ile Gln met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys FR2: Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Pro Leu Ile Tyr FR3: Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser reu Gln Pro Clu Asp lie Ala Txr Tyr Tyr Cys FR4: Phe Gly Gln Gly Thr Lys Val Glu Ile Lys (2) FR1: Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys FR2: Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Pro Leu Ile Tyr FR3: Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys FR4: Phe Gly Gln Cly Thr Lys Val Glu Ile Lys

10. An L chain according to claim 2 wherein said human L chain C region is a KC region.

11. An H chain V region of an antibody to human medulloblastoma cells containing three CDRs having the amino acid sequences defined below: CDR1; Asp Thr Tyr Ile His CDR2: Arg Ile Asp Pro Ala Asp Gly Asn Thr Lys Tyr Asp Pro Lys Phe Gln Gly CDR3: Ala Tyr Tyr Val Asn Gln Asp Tyr or a portion thereof and four FRs.

12. An H chain of antibody to human medulloblastoma cells comprising the H chain V region of claim 11 and a human H C region.

13. An H chain according to claim 12 wherein the FRs of said H chain V region are derived from a mouse antibody.

14. The H chain according to claim 12 wherein said H chain V region has the amino acid sequence indicated in SEQ ID NO:27.

15. An H chain according to claim 12 wherein the FRs of said H chain V region are derived from a human antibody.

16. An H chain according to claim 12 or 15 wherein the FRs of said H chain V region are derived from a human antibody of subgroup I.

17. An H chain according to claim 12 or 15 wherein the FRs of said H chain V region are derived from a human antibody Eu.

18. The H chain according to claim 15 wherein said H chain V region contains four FRs having the following amino acid sequences; FR1: Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Ws Lys Ala Ser Gly Phe Asn Ile Lys FR2: Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly FR3: Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr Met Glu Leu Ser Ser beu Arg Ser Glu Asp Thr Ala Phe Tyr Phe Cys Ala Ser FR4: Trp Gly Gln Gly Thr Thr Val Thr Val Sor Ser

19. The H chain according to claim 15 wherein said human C region is a γ-1C region or γ-4C region.

20. An antibody to human medulloblastoma cells composed of the L chain as set forth in claim 2 and the H chain as set forth in claim 12.

21. An antibody according to claim 20 wherein the FRs of said V region are derived from a mouse antibody.

22. The antibody as set forth in claim 20 wherein the FRs of said V region are derived from a human antibody.

23. A DNA coding for an L chain of an antibody to human medulloblastoma cells comprising an L chain V region containing three CDRs having the amino acids as set forth in claim 1 or a portion thereof and four FRs, and a human L chain C region.

24. A DNA according to claim 23 wherein said L chain V region has a nucleotide sequence indicated in SEQ ID NO:58, 61, 63, 66, 70 or 73.

25. A DNA coding for an H chain of an antibody to human medulloblastoma cells comprising an H chain V region containing three CDRs having the amino acids as set forth in claim 11 or a portion thereof and four FRs, and a human H chain C region.

26. A DNA according to claim 25 wherein said H chain V region has the nucleotide sequence indicated in SEQ ID NO:80.

27. A recombinant vector comprising a DNA according to claim 23 or 24 or a portion thereof.

28. A recombinant vector comprising a DNA according to claim 25 or 26 or a portion thereof.

29. A transformant co-transformed with a recombinant vector according to claim 27 and the recombinant vector as set forth in claim 28.

30. A process for producing antibody to human medulloblastoma cells using gene recombination technology comprising a culturing a transformant according to claim 29 and then isolating a target antibody produced.

31. A single-chain Fv composed by linking an H chain V region according to claim 11 with an L chain V region as set forth in claim I by means of a peptide **linker**.

32. A single-chain Fv according to claim 31 wherein said **linker** peptide has the following amino acid sequence: Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser

33. A single-chain Fv according to claim 31 or 32 comprising an H chain V region having an amino acid sequence of amino acid numbers from 1 to 116 in the amino acid sequence set forth in SEQ ID NO:80, and an L chain V region having an amino acid sequence of amino acid numbers from 1 to 106 in the amino acid sequence set forth in SEQ ID NO:40, 43, 46, 47, 50, 51, 54, 55, 58, 61, 62. 63, 66, 69, 70 or 73.

34. A single-chain Pv according to claim 31 or 32 comprising an H chain V region having an amino acid sequence of amino acid numbers from 1 to 116 i:: the amino acid sequence set forth in SEQ ID NO. 80, and an L chain V region having an amino acid sequence of amino acid numbers from 1 to 106 in the amino acid sequence set forth in SEQ ID NO:73.

35. A single-chain Fv according to claim 31 having an amino acid sequence as set forth in SEQ ID NO; 39.

36. A DNA coding for a single-chain Fv according to any one of claims 31 to 35.

37. A recombinant vector comprising a DNA according to claim 36.

38. A host transfected with a recombinant vector according to claim 37.

39. A process for producing a single-chain Fv comprising culturing a transformant according To claim 38 and recovering single-chain Fv region from said culture.

L19 ANSWER 10 OF 11 USPATFULL on STN
2000:24470 Monoclonal antibody to a human MDR1 multidrug resistance gene product, and uses.
Metchetner, Eugene, Palo Alto, CA, United States
Roninson, Igor B., Wilmette, IL, United States
University of Illinois, Urbana, IL, United States (U.S. corporation)
US 6030796 20000229
APPLICATION: US 1995-482670 19950607 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A cDNA sequence encoding a recombinantly-produced protein that is a chimeric monoclonal antibody having a V_H and V_L chain of UIC2 monoclonal antibody (A.T.C.C. Accession No. HB11027) or antigen binding fragment thereof and a constant region of a human immunoglobulin.

2. A prokaryotic or eukaryotic cell containing a recombinant expression vector comprising a cDNA sequence of claim 1.

3. A protein expressed by a cell according to claim 2, wherein the protein has an antigen-binding specificity of the UIC2 monoclonal

antibody.

4. A cDNA sequence encoding a recombinantly-produced protein that is a single chain monoclonal antibody having a VH and VL chain having an amino acid sequence of the antibody produced by a hybridoma cell line identified by ATCC Accession Number HB11027 or antigen-binding fragment thereof linked by a flexible, peptide **linker**.

5. A prokaryotic or eukaryotic cell containing a recombinant expression vector encoding a cDNA sequence of claim 4.

6. A cDNA sequence encoding a recombinantly-produced protein that is a humanized monoclonal antibody having **complementarity-determining regions** having an amino acid sequence of the antibody produced by a hybridoma cell line identified by ATCC Accession Number HB11027 or antigen-binding fragment thereof grafted onto a human antibody.

7. A prokaryotic or eukaryotic cell containing a recombinant expression vector encoding a cDNA sequence of claim 6.

8. A cDNA sequence encoding a recombinantly-produced protein that is a fusion protein comprising a **complementarity-determining region** having an amino acid sequence of the antibody produced by a hybridoma cell line identified by ATCC Accession Number HB11027 or antigen-binding fragment thereof, wherein the fusion protein is expressed on the surface of a prokaryotic cell, a eukaryotic cell, a bacteriophage or a eukaryotic virus.

9. A prokaryotic or eukaryotic cell containing a recombinant expression vector encoding a cDNA sequence of claim 8.

10. A cDNA sequence encoding a recombinantly-produced protein that is a protein selected from the group consisting of a combination of a heavy chain and a light chain of UIC2 monoclonal antibody produced by a hybridoma cell line identified by ATCC Accession Number HB11027 or Fab, Fab', F(ab)2 or Fv fragment thereof, a combination of a variable region ofthe heavy chain (VH) and a variable region ofthe light chain (VL) of UIC2 monoclonal antibody, and a combination of a complementarity-determining portion of the VH region and a **framework region** and a complementarity-determining portion of the VL region and the **framework region** of UIC2 monoclonal antibody, wherein said combination forms a protein that specifically binds an epitope of a human multidrug resistance protein.

11. A prokaryotic or eukaryotic cell containing a recombinant expression vector encoding a CDNA sequence of claim 10.

12. A composition of matter comprising a prokaryotic cell, a bacteriophage, a eukaryotic cell or a eukaryotic virus wherein a **complementarity-determining region** of an antibody having an amino acid sequence of the antibody produced by a hybridoma cell line identified by ATCC Accession Number HB 11027, or antigen-binding fragment thereof, is expressed on the surface thereof.

13. A hybrid hybridoma produced by fusing a hybridoma cell identified by ATCC Accession Number HB11027 with another, non-UIC2 monoclonal antibody-producing cell selected from the group consisting of a second hybridoma cell, a spleen cell, an activated peripheral blood lymphocyte and a cultured lymphocyte.

14. A monoclonal antibody produced by a hybrid cell line of claim 13.

15. An anti-idiotype antibody of the antibody produced by a hybridoma identified by ATCC Accession Number HB11027.

16. A method for detecting multidrug resistant primate tumor cells comprising the steps of contacting said tumor cells or lysates thereof with a reagent that is operably linked to a reporter molecule and comprises an antibody selected from the group consisting of the UIC2 monoclonal antibody, an antigen-binding fragment of the UIC2 monoclonal antibody, and a recombinantly produced protein encoded by a cDNA according to claim 7, and detecting said reporter molecule.

17. A composition comprising an antibody selected from the group consisting of the UIC2 monoclonal antibody produced by a hybridoma cell line identified by A.T.C.C. Accession No. HB11027, an antigen-binding fragment of UIC2 monoclonal antibody and a recombinantly-produced UIC2 monoclonal antibody, and a pharmaceutically acceptable vehicle.

18. A composition of claim 17, further comprising a cytotoxin or radioisotope or both, covalently conjugated to said UIC2 monoclonal antibody, antigen-binding fragment of UIC2 monoclonal antibody or recombinantly-produced monoclonal antibody.

19. A composition of claim 17 further comprising an admixed anti-tumor effective amount of an anti-cancer cytotoxic drug.

20. A composition of claim 18 further comprising an admixed anti-tumor effective amount of an anti-cancer cytotoxic drug.

21. A method for isolating multidrug resistant primate cells, comprising the steps of: a) contacting a sample comprising said cells with an immunoaffinity purification reagent comprising an antibody selected from the group consisting of the UIC2 monoclonal antibody produced by a hybridoma cell line identified by ATCC Accession Number HB11027, and antigen-binding fragment of UIC2 monoclonal antibody, and a recombinantly-produced UIC2 monoclonal antibody, wherein said antibody is operably linked to a solid support, to form an immobilized cell-antibody complex: and, b) recovering adsorbed cells from said complex.

22. A method for isolating a human mdr1 gene product from a mixture of biomolecules, comprising the steps of: a) contacting an immunoaffinity purification reagent comprising an antibody selected from the group consisting of the UIC2 monoclonal antibody produced by a hybridoma cell line identified by ATCC Accession Number HB11027, an antigen-binding fragment of UIC2 monoclonal antibody, and a recombinantly-produced UIC2 monoclonal antibody, wherein said antibody is operably linked to a solid support, with said mixture of biomolecules to form an immobilized antibody human mdr1 gene product complex; and b) recovering said human mdr1 gene product from said immobilized complex.

23. A method of isolating human MDR P-glycoprotein from a cell membrane carrying same, comprising the steps of: a) contacting said cell P-glycoprotein with an antibody selected from the group consisting of UIC2 monoclonal antibody produced by a hybridoma cell line identified by ATCC Accession Number HB11027, an antigen-binding fragment of UIC2 monoclonal antibody, and a recombinantly-produced UIC2 monoclonal antibody to form a P-glycoprotein-antibody complex, wherein said contacting is performed either before or after solubilizing said cell membrane with a detergent; b) separating the solubilized P-glycoprotein-antibody complex from the remainder of the solubilized cell material; and, c) recovering said P-glycoprotein from said solubilized complex.

24. A method of claim 23 wherein said detergent is deoxycholate or N-octylglucoside.

25. A method of claim 23 wherein said solubilized complex is separated in step b) by adsorption to immobilized Protein A.

26. A method of claim 23 wherein optionally said antibody is pre-adsorbed to Protein A-coated beads prior to contact with cell P-glycoprotein.

L19 ANSWER 11 OF 11 USPATFULL on STN
1999:136681 Composite antibodies of human subgroup IV light chain capable of binding to tag-72.
Mezes, Peter S., Oldlyme, CT, United States
Richard, Ruth A., Midland, MI, United States
Johnson, Kimberly S., New London, CT, United States
The Dow Chemical Company, Midland, MI, United States (U.S. corporation)
US 5976531 19991102
APPLICATION: US 1994-261354 19940616 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A Hum4 VL, VH antibody which specifically binds to TAG-72, or an antigen-binding fragment thereof, consisting essentially of at least one light chain variable region (VL) and at least one heavy chain variable region (VH) wherein (a) the VL is a human kappa Subgroup IV VL encoded by the human Subgroup IV germline gene (Hum4 VL) or by one of the effectively homologous human kappa Subgroup IV genes or DNA sequences thereof, the VL comprising human **complementarity determining regions** (CDRs) and human kappa Subgroup IV **framework regions**; (b) the VH is an anti-TAG-72 VH encoded by a DNA sequence encoding, as said VH, at least the heavy chain variable region of an antibody which specifically binds TAG-72; and the VH is capable of combining with the VL to form a three dimensional structure having the ability to specifically bind TAG-72.

2. The Hum4 VL, VH antibody or fragment thereof of claim 1, wherein the VL is further encoded by a human J gene segment.

3. The Hum4 VL, VH antibody or fragment thereof of claim 1 wherein the VH is encoded by a DNA sequence which comprises the VH αTAG germline gene or one of its effectively homologous genes or productively rearranged derivatives.

4. The Hum4 VL, VH antibody or fragment thereof of claim 1, wherein the VH is further encoded by a mammalian D gene segment.

5. The Hum4 VL, VH antibody or fragment thereof of claim 1, wherein the VH is derived from the variable regions of CC46, CC49, CC83 or CC92.

6. The Hum4 VL, VH antibody or fragment thereof of claim 1, wherein the VH comprises (I) CDRs encoded by a gene derived from the VH αTAG, and (2) framework segments, adjacent to the CDRs, encoded by a human gene.

7. The Hum4 VL, VH antibody or fragment thereof of claim 1, wherein the light chain further comprises at least a portion of a human constant region (CL) and the heavy chain further comprises at least

a portion of a mammalian constant region (CH).

8. The Hum4 VL, VH antibody or fragment thereof of claim 7, wherein the CH is human IgG1-4, IgM, IgA1, IgA2, IgD or IgE.

9. The Hum4 VL, VH antibody or fragment thereof of claim 7, wherein CL is kappa or lambda.

10. The Hum4 VL, VH antibody or fragment thereof of claim 1 wherein the antibody is MP1-44H produced by a cell line having the identifying characteristics of ATCC HB 10426 or MP1-84H produced by a cell line having the identifying characteristics of ATCC HB 10427.

11. A Hum4 VL, VH antibody conjugate comprising the Hum4 VL, VH antibody or fragment thereof of claim 1 conjugated to an imaging marker or a therapeutic agent.

12. The Hum4 VL, VH antibody conjugate of claim 11, wherein the imaging marker is selected from the group consisting of 125 I, 131 I, 123 I, 111 In, 105 Rh, 153 Sm, 67 Cu, 67 Ga, 166 Ho, 177 Lu, 186 Re, 188 Re, and 99m Tc.

13. The Hum4 VL, VH antibody conjugate of claim 11, wherein the therapeutic agent is a drug or biological response modifier, radionuclide, or toxin.

14. The Hum4 VL, VH antibody conjugate of claim 13, wherein the drug is methotrexate, adriamycin or interferon.

15. The Hum4 VL, VH antibody conjugate of claim 13, wherein the radionuclide is 131 I, 90 Y, 105 Rh, 47 Sc, 67 Cu, 212 Bi, 211 At, 67 Ga, 125 I, 186 Re, 188 Re, 177 Lu, 99m Tc, 153 Sm, 123 I or 111 In.

16. A composition for cancer treatment comprising a pharmaceutically effective amount of the Hum4 VL, VH antibody or fragment thereof of claim 1 in a pharmaceutically acceptable, non-toxic, sterile carrier.

17. A composition for cancer treatment comprising a pharmaceutically effective amount of the Hum4VL, VH antibody conjugate of claim 12 in a pharmaceutically acceptable, non-toxic, sterile carrier.

18. A composition for cancer treatment comprising a pharmaceutically effective amount of the Hum4VL, VH antibody conjugate of claim 13 in a pharmaceutically acceptable, non-toxic, sterile carrier.

19. The Hum4 VL, VH antibody or fragment thereof of claim 4, wherein the VH is further encoded by a mammalian gene segment.

20. A Hum4 VL, VH single chain antibody which specifically binds to TAG-72, or an antigen-binding fragment thereof, consisting essentially of (a) at least one light chain having a variable region (VL), said VL being a human kappa Subgroup IV VL, encoded by the human Subgroup IV germline gene (Hum4 VL) or by one of the effectively homologous human kappa Subgroup IV genes or DNA sequences thereof, the VL comprising human CDRs and human kappa Subgroup IV **framework regions**; (b) at least one heavy chain having a variable region (VH), said VH being an anti-TAG-72 VH encoded by a DNA sequence encoding, as said VH, at least the heavy chain

variable region of an antibody which specifically binds TAG-72; and (c) at least one polypeptide **linker** linking the VH and VL, wherein the VH is capable of combining with the VL to form a three dimensional structure having the ability to bind TAG-72 and the polypeptide **linker** allows the proper folding of the VH and VL into a single chain antibody which is capable of forming said three-dimensional structure.

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=> d his

     (FILE 'HOME' ENTERED AT 20:15:09 ON 27 SEP 2006)

     FILE 'USPATFULL' ENTERED AT 20:15:17 ON 27 SEP 2006
                E HUSTON JAMES S/IN
L1           26 S E3
L2            7 S L1 AND (FRAMEWORK REGION?/CLM)
                E OPPERMANN H/AU
                E E12
L3          101 S E3-E5
L4           84 S L3 NOT L1
L5            0 S L4 AND (FRAMEWORK REGION?/CLM)

     FILE 'WPIDS' ENTERED AT 20:20:02 ON 27 SEP 2006
                E HUSTON J S/IN
L6           20 S E3
L7            9 S L6 AND (FRAMEWORK REGION?)
                E OPPERMANN H/IN
L8          138 S E3
L9          126 S L8 NOT L6
L10           0 S L9 AND (FRAMEWORK REGION?)

     FILE 'MEDLINE' ENTERED AT 20:23:24 ON 27 SEP 2006
                E HUSTON J S/AU
L11          35 S E3
L12           0 S L11 AND (FRAMEWORK REGION?)
                E OPPERMANN H/AU
L13          75 S E3
L14          65 S L13 NOT L11
L15           1 S L14 AND (FRAMEWORK)

     FILE 'USPATFULL' ENTERED AT 20:32:29 ON 27 SEP 2006
L16         380 S (FRAMEWORK REGION?/CLM)
L17         197 S L16 AND (COMPLEMENTARITY DETERMINING REGION?/CLM)
L18          17 S L17 AND LINKER/CLM
L19          11 S L18 NOT L1

=> s (biosynthetic antibody binding site?/clm or BABS/clm)
          702 BIOSYNTHETIC/CLM
        38004 ANTIBODY/CLM
        62046 BINDING/CLM
        72360 SITE?/CLM
           10 BIOSYNTHETIC ANTIBODY BINDING SITE?/CLM
                ((BIOSYNTHETIC(W)ANTIBODY(W)BINDING(W)SITE?)/CLM)
            6 BABS/CLM
L20         16 (BIOSYNTHETIC ANTIBODY BINDING SITE?/CLM OR BABS/CLM)

=> s l20 not l1
L21         15 L20 NOT L1

=> s l21 not l19
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L22 15 L21 NOT L19

=> d l22,cbib,clm,1-15

L22 ANSWER 1 OF 15 USPATFULL on STN
2006:248245 Immunostimulatory nucleic acids and cancer medicament combination therapy for the treatment of cancer.
Bratzler, Robert L., Concord, MA, UNITED STATES
Petersen, Deanna M., Newton, MA, UNITED STATES
US 2006211639 A1 20060921
APPLICATION: US 2003-668050 A1 20030922 (10)
PRIORITY: US 2000-187214P 20000303 (60)
DOCUMENT TYPE: Utility; APPLICATION.

CLM What is claimed is:

1. A method for treating a subject having, or at risk of developing, a cancer, comprising: administering to a subject in need of such treatment a poly-G nucleic acid and a cancer medicament in an effective amount to treat the cancer or to reduce the risk of developing the cancer, wherein the poly-G nucleic acid is not conjugated to the cancer medicament.

2. The method of claim 1, wherein the cancer medicament is selected from the group consisting of a chemotherapeutic agent, an immunotherapeutic agent, and a cancer vaccine.

3. The method of claim 2, wherein the chemotherapeutic agent is selected from the group consisting of methotrexate, vincristine, adriamycin, cisplatin, non-sugar containing chloroethylnitrosoureas, 5-fluorouracil, mitomycin C, bleomycin, doxorubicin, dacarbazine, taxol, fragyline, Meglamine GLA, valrubicin, carmustaine and poliferposan, MM1270, BAY 12-9566, RAS famesyl transferase inhibitor, famesyl transferase inhibitor, MMP, MTA/LY231514, LY264618/Lometexol, Glamolec, CI-994, TNP-470, Hycamtin/Topotecan, PKC412, Valspodar/PSC833, Novantrone/Mitroxantrone, Metaret/Suramin, Batimastat, E7070, BCH-4556, CS-682, 9-AC, AG3340, AG3433, Incel/VX-710, VX-853, ZD0101, IS1641, ODN 698, TA 2516/Marmistat, BB2516/Marmistat, CDP 845, D2163, PD183805, DX8951f, Lemonal DP 2202, FK 317, Picibanil/OK-432, AD 32/Valrubicin, Metastron/strontium derivative, Temodal/Temozolomide, Evacet/liposomal doxorubicin, Yewtaxan/Placlitaxel, Taxol/Paclitaxel, Xeload/Capecitabine, Furtulon/Doxifluridine, Cyclopax/oral paclitaxel, Oral Taxoid, SPU-077/Cisplatin, HMR 1275/Flavopiridol, CP-358 (774)/EGFR, CP-609 (754)/RAS oncogene inhibitor, BMS-182751/oral platinum, UFT(Tegafur/Uracil), Ergamisol/Levamisole, Eniluracil/776C85/5FU enhancer, Campto/Levamisole, Camptosar/Irinotecan, Tumodex/Ralitrexed, Leustatin/Cladribine, Paxex/Paclitaxel, Doxil/liposomal doxorubicin, Caelyx/liposomal doxorubicin, Fludara/Fludarabine, Pharmarubicin/Epirubicin, DepoCyt, ZD1839, LU 79553/Bis-Naphtalimide, LU 103793/Dolastain, Caetyx/liposomal doxorubicin, Gemzar/Gemcitabine, ZD 0473/Anormed, YM 116, Iodine seeds, CDK4 and CDK2 inhibitors, PARP inhibitors, D4809/Dexifosamide, Ifes/Mesnex/Ifosamide, Vumon/Teniposide, Paraplatin/Carboplatin, Plantinol/cisplatin, Vepeside/Etoposide, ZD 9331, Taxotere/Docetaxel, prodrug of guanine arabinoside, Taxane Analog, nitrosoureas, alkylating agents such as melphelan and cyclophosphamide, Aminoglutethimide, Asparaginase, Busulfan, Carboplatin, Chlorombucil, Cytarabine HCl, Dactinomycin, Daunorubicin HCl, Estramustine phosphate sodium, Etoposide (VP16-213), Floxuridine, Fluorouracil (5-FU), Flutamide, Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alfa-2a, Alfa-2b, Leuprolide acetate (LHRH-releasing factor analogue), Lomustine (CCNU), Mechlorethamine HCl (nitrogen mustard), Mercaptopurine, Mesna, Mitotane (o.p'-DDD), Mitoxantrone HCl, Octreotide, Plicamycin, Procarbazine HCl, Streptozocin, Tamoxifen citrate, Thioguanine, Thiotepa, Vinblastine

sulfate, Amsacrine (m-AMSA), Azacitidine, Erthropoietin, Hexamethylmelamine (HMM), Interleukin 2, Mitoguazone (methyl-GAG; methyl glyoxal bis-guanylhydrazone; MGBG), Pentostatin (2'deoxycoformycin), Semustine (methyl-CCNU), Teniposide (VM-26) and Vindesine sulfate.

4. The method of claim 2, wherein the immunotherapeutic agent is selected from the group consisting of Ributaxin, Herceptin, Quadramet, Panorex, IDEC-Y2B8, BEC2, C225, Oncolym, SMART M195, ATRAGEN, Ovarex, Bexxar, LDP-03, ior t6, MDX-210, MDX-11, MDX-22, OV103, 3622W94, anti-VEGF, Zenapax, MDX-220, MDX-447, MELIMMUNE-2, MELIMMUNE-1, CEACIDE, Pretarget, NovoMAb-G2, TNT, Gliomab-H, GNI-250, EMD-72000, LymphoCide, CMA 676, Monopharm-C, 4B5, ior egf.r3, ior c5, **BABS**, anti-FLK-2, MDX-260, ANA Ab, SMART 1D10 Ab, SMART ABL 364 Ab and ImmuRAIT-CEA.

5. The method of claim 2, wherein the cancer vaccine is selected from the group consisting of EGF, Anti-idiotypic cancer vaccines, Gp75 antigen, GMK melanoma vaccine, MGV ganglioside conjugate vaccine, Her2/neu, Ovarex, M-Vax, O-Vax, L-Vax, STn-KHL theratope, BLP25 (MUC-1), liposomal idiotypic vaccine, Melacine, peptide antigen vaccines, toxin/antigen vaccines, MVA-based vaccine, PACIS, BCG vacine, TA-HPV, TA-CIN, DISC-virus and ImmuCyst/TheraCys.

6. The method of claim 1, wherein the cancer medicament is a hormone therapy.

7. The method of claim 1, wherein the cancer medicament is taxol.

8. The method of claim 1, further comprising administering interferon-α to the subject.

9. The method of claim 1, wherein the cancer is selected from the group consisting of bone cancer, brain and CNS cancer, connective tissue cancer, esophageal cancer, eye cancer, Hodgkin's lymphoma, larynx cancer, oral cavity cancer, skin cancer, and testicular cancer.

10. The method of claim 1, wherein the immunostimulatory nucleic acid has a modified backbone.

11. The method of claim 10, wherein the modified backbone is a phosphorothioate modified backbone.

12. A method for treating a subject having or at risk of developing a cancer, comprising: administering to a subject in need of such treatment, an immunostimulatory nucleic acid having a modified backbone and a cancer medicament selected from the group consisting of an immunotherapeutic agent, a cancer vaccine and a hormone therapy, wherein the immunostimulatory nucleic acid is free of a CpG motif, and a T-rich motif.

13. The method of claim 12, wherein the immunostimulatory nucleic acid is a poly-G nucleic acid.

14. The method of claim 13, wherein the poly-G nucleic acid is not conjugated to the cancer medicament.

15. The method of claim 12, wherein the cancer medicament is taxol.

16. The method of claim 12, further comprising administering interferon-α to the subject.

17. The method of claim 12, further comprising administering a cancer antigen to the subject.

18.-20. (canceled)

21. A method for preventing an allergic reaction in a subject receiving a blood transfusion, comprising administering to a subject receiving a blood transfusion an immunostimulatory nucleic acid in an effective amount to prevent an allergic reaction to the blood transfusion.

22.-30. (canceled)

31. A method for treating a subject having or at risk of developing cancer, comprising administering to a subject in need of such treatment an immunostimulatory nucleic acid selected from the group consisting of a CpG nucleic acid and a non-CpG nucleic acid, and a cancer medicament that is a hormone therapy.

32.-35. (canceled)

36. A device for delivering an immunostimulatory nucleic acid to a subject receiving an intravenous injection, comprising an intravenous device selected from the group consisting of an intravenous bag and an intravenous tube, and an immunostimulatory nucleic acid, wherein the immunostimulatory nucleic acid is coated on an internal surface of the intravenous device or is embedded within the intravenous device.

37. A method for treating a subject having cancer comprising administering to the subject an immunostimulatory nucleic acid in a colloidal dispersion system, wherein the immunostimulatory nucleic acid is 8-100 nucleotides in length, and wherein the subject is receiving or has received radiation.

38. The method of claim 37, wherein the immunostimulatory nucleic acid is a CpG nucleic acid.

39. The method of claim 38, wherein the colloidal dispersion system is a liposome.

40. The method of claim 39, wherein the immunostimulatory nucleic acid is administered following radiation.

41. A method comprising administering an immunostimulatory nucleic acid in an implant to a subject that is receiving radiation, wherein the nucleic acid is 8-100 nucleotides in length.

42. The method of claim 41, wherein the immunostimulatory nucleic acid is a CpG nucleic acid.

43. The method of claim 41, further comprising stimulating an immune response in the subject.

44. The method of claim 41, wherein the subject has cancer.

45. The method of claim 44, wherein the cancer is basal cell carcinoma, biliary tract cancer, bladder cancer, bone cancer, brain cancer, CNS cancer, breast cancer, cervical cancer, choriocarcinoma, colon and rectum cancer, connective tissue cancer, cancer of the digestive system, endometrial cancer, esophageal cancer, eye cancer, cancer of the head and neck, gastric cancer, intra-epithelial neoplasm; kidney cancer, larynx cancer, leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, lymphoma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, melanoma, myeloma, neuroblastoma, oral cavity cancer, ovarian cancer, pancreatic cancer, prostate cancer, retinoblastoma, rhabdomyosarcoma,

rectal cancer, renal cancer, cancer of the respiratory system, sarcoma, skin cancer, stomach cancer, testicular cancer, thyroid cancer, uterine cancer, cancer of the urinary system, as well as other carcinomas and sarcomas.

46. The method of claim 41, wherein the nucleic acid is administered following radiation.

47. The method of claim 41, wherein the nucleic acid is synthetic

48. A kit comprising an immunostimulatory nucleic acid and a chemical/physical vector, wherein the nucleic acid is 8-100 nucleotides in length.

49. The kit of claim 48, wherein the chemical/physical vector is an implant.

50. The kit of claim 48, further comprising a cancer medicament, wherein the cancer medicament is a chemotherapy.

51. A method of treating a subject with cancer comprising: administering at least one ligand for a pattern recognition receptor and a delivery vehicle; in conjunction with at least one cancer therapy wherein said method elicits a response in a subject disposed of cancer.

52. The method of claim 51, wherein said cancer therapy comprises at least one therapy consisting of hyperthermia therapy, radiation therapy, chemotherapy, photodynamic therapy (PDT), surgery, ultrasound, and focused ultrasound.

53. The method of claim 52, wherein radiation therapy is introduced first.

54. The method of claim 51, wherein the pattern recognition receptor ligand comprises a nucleic acid molecule.

55. The method of claim 51, wherein the delivery vehicle comprises a liposome.

56. The method of claim 51, wherein the delivery vehicle comprises a non-liposomal delivery vehicle.

57. A method comprising: coating a medical device with a composition comprising at least one ligand for a pattern recognition molecule receptor; and a delivery vehicle.

58. The method of claim 57, wherein the medical device comprises an implanted device.

59. The method of claim 58, wherein the implanted device consists of at least one of the following devices consisting of a catheter, a stent, a mesh repair material, a Dacron vascular prothesis, a orthopedic metallic plate, a rod and a screws.

60. The method of claim 57, wherein the delivery device comprises a sustained release particle and a delivery vehicle.

61. The method of claim 60, wherein the delivery vehicle comprises a liposome.

62. A method comprising: administering a composition comprising at least one ligand for a pattern recognition molecule receptor; a delivery

device; and radiation therapy to a subject.

63. The method of claim 62, wherein a ligand for a pattern recognition molecule receptor comprises a ligand for a signaling pattern recognition receptor.

64. The method of claim 62, wherein a ligand for a pattern recognition molecule receptor comprises a ligand for an pattern recognition receptor.

65. The method of claim 62, further comprising augmenting an immune response in said subject.

66. The method of claim 65, wherein augmenting an immune response comprises augmenting an immune response in a subject disposed of cancer.

67. The method of claim 66, wherein cancer comprises at least one cancer selected from the group consisting of lung cancer, skin cancer, liver cancer, bone marrow cancer, brain cancer, renal cell cancer, ovarian cancer, breast cancer, prostate cancer, cancers of mesenchymal tissues, lymphoma and colon cancer.

68. The method of claim 62, wherein radiation therapy is introduced first.

69. The method of claim 62, wherein the ligand comprises a synthetic compound capable of binding a pattern recognition receptor.

70. A kit comprising: a delivery container; a delivery device; at least one ligand for a pattern recognition receptor; and plus or minus an antigen; wherein said ligand is capable of eliciting an immune response in a subject.

71. The kit of claim 70, further comprising one or more chemotherapy agents.

L22 ANSWER 2 OF 15 USPATFULL on STN
2006:188717 Materials and methods for detection and treatment of breast cancer.
Watkins, Brynmor, Newton, MA, UNITED STATES
Szaro, Robert P., Norwood, MA, UNITED STATES
Matritech, Inc., Newton, MA, UNITED STATES (U.S. corporation)
US 2006160154 A1 20060720
APPLICATION: US 2005-194051 A1 20050729 (11)
PRIORITY: US 1999-165673P 19991116 (60)
US 1999-172170P 19991217 (60)
US 2000-178860P 20000127 (60)
US 2000-201721P 20000503 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1-42. (canceled)

43. A method of diagnosing breast cancer in a mammal, the method comprising the steps of: (a) obtaining a sample isolated from the mammal; and (b) detecting in the sample the presence or absence of a protein characterized as comprising an amino acid sequence selected from the group consisting of SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO: 1; SEQ ID NO:12; SEQ ID NO:13; SEQ ID NO:14; SEQ ID NO:15; SEQ ID NO:16; SEQ ID NO:17; SEQ ID NO:18; SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:22; and SEQ ID NO:23, wherein the presence of the protein is indicative of the presence of

breast cancer in the mammal, and wherein the absence of the protein is indicative of the absence of breast cancer in the mammal.

44. (canceled)

45. The method of claim 43 or 70, wherein the sample comprises breast tissue.

46. The method of claim 43 or 70, wherein the sample comprises a body fluid.

47. The method of claim 46, wherein the body fluid is selected from the group consisting of blood, serum, plasma, sweat, tears, urine, peritoneal fluid, lymph, vaginal secretions, semen, spinal fluid, ascitic fluid, saliva, sputum, and breast exudate.

48. A method of diagnosing breast cancer in a mammal, the method comprising the steps of: (a) contacting a sample derived from the mammal with a binding moiety that binds specifically to a protein comprising an amino acid sequence of SEQ ID NO:23, thereby to produce a complex; and (b) detecting the presence or absence of the complex, wherein the presence of the complex is indicative of the presence of breast cancer in the mammal and wherein the absence of the complex is indicative of the absence of breast cancer in the mammal.

49. (canceled)

50. The method of claim 48 or 71, wherein the binding moiety is selected from the group consisting of an antibody, an antibody fragment and a **biosynthetic antibody binding site**.

51. The method of claim 48 or 71, wherein the binding moiety is an antibody.

52. The method of claim 51, wherein the antibody is a monoclonal antibody.

53. The method of claim 50, wherein the binding moiety is labeled with a detectable moiety.

54. The method of claim 48, wherein the absence of a detectable amount of the complex is indicative of the absence of breast cancer.

55-62. (canceled)

63. The method of claim 46, wherein the body fluid is serum.

64. The method of claim 48 or 71, wherein the sample comprises breast tissue.

65. The method of claim 48 or 71, wherein the sample comprises a body fluid.

66. The method of claim 65, wherein the body fluid is selected from the group consisting of blood, serum, plasma, sweat, tears, urine, peritoneal fluid, lymph, vaginal secretions, semen, spinal fluid, ascitic fluid, saliva, sputum, and breast exudate.

67. The method of claim 65, wherein the body fluid is serum.

68. The method of claim 43, wherein the presence of a detectable amount of the protein is indicative of the presence of breast cancer in the

mammal.

69. The method of claim 43, wherein the absence of a detectable amount of the protein is indicative of the absence of breast cancer in the mammal.

70. A method of diagnosing breast cancer in a mammal, the method comprising the step of: determining whether a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13; SEQ ID NO:14; SEQ ID NO:15; SEQ ID NO:16; SEQ ID NO:17; SEQ ID NO:18; SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:22; and SEQ ID NO:23 is present in a sample derived from the mammal in an amount greater than or equal to a threshold value indicative of the presence of breast cancer in the mammal, wherein an amount of protein greater than or equal to the threshold value is indicative of the presence of breast cancer in the mammal and an amount of protein less than the threshold value is indicative of the absence of breast cancer in the mammal.

71. A method of diagnosing breast cancer in a mammal, the method comprising the steps of: (a) contacting a sample from the mammal derived from the mammal with a binding moiety that binds specifically to a protein comprising an amino acid sequence of SEQ ID NO:23, thereby to produce a complex; and (b) determining whether the complex is present in an amount greater than or equal to a threshold value indicative of the presence of breast cancer in the mammal, wherein an amount greater than or equal to the threshold value is indicative of the presence of breast cancer in the mammal and an amount less than the threshold value is indicative of the absence of breast cancer in the mammal.

L22 ANSWER 3 OF 15 USPATFULL on STN
2005:217313 Materials and methods for detection and treatment of breast cancer.
Watkins, Brynmor, Waltham, MA, UNITED STATES
Szaro, Robert P., Franklin, MA, UNITED STATES
Matritech, Inc., Newton, MA, UNITED STATES (U.S. corporation)
US 6936424 B1 20050830
APPLICATION: US 2000-709947 20001110 (9)
PRIORITY: US 2000-201721P 20000503 (60)
US 2000-178860P 20000127 (60)
US 1999-172170P 19991217 (60)
US 1999-165173P 19991112 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of diagnosing breast cancer in a mammal, the method comprising the steps of: (a) obtaining a sample isolated from the mammal; and (b) detecting in the sample the presence or absence of a protein characterized as comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 1; SEQ ID NO: 2; SEQ ID NO: 3; SEQ ID NO: 4; and SEQ ID NO: 5, wherein the presence of the protein is indicative of the presence of breast cancer in the mammal, and wherein the absence of the protein is indicative of the absence of breast cancer in the mammal.

2. A method of diagnosing breast cancer in a mammal, the method comprising the step of: determining whether a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, and SEQ ID NO:5 is present in a sample derived from the mammal in an amount greater than or equal to a threshold value indicative of the presence of breast cancer in the

mammal, wherein an amount of protein greater than or equal to the threshold value is indicative of the presence of breast cancer in the mammal and an amount of protein less than the threshold value is indicative of the absence of breast cancer in the mammal.

3. The method of claim 1 or 2, wherein the sample comprises breast tissue.

4. The method of claim 1 or 2, wherein the sample comprises a body fluid.

5. The method of claim 4, wherein the body fluid is selected from the group consisting of blood, serum, plasma, sweat, tears, urine, peritoneal fluid, lymph, vaginal secretions, semen, spinal fluid, ascitic fluid, saliva, sputum, and breast exudate.

6. A method of diagnosing breast cancer in a mammal, the method comprising the steps of: (a) contacting a sample derived from the mammal with a binding moiety that binds specifically to a protein comprising an amino acid sequence of SEQ ID NO: 5, thereby to produce a complex; and (b) detecting the presence or absence of a complex, wherein the presence of the complex is indicative of the presence of breast cancer in the mammal, and wherein the absence of the complex is indicative of the absence of breast cancer in the mammal.

7. A method of diagnosing breast cancer in a mammal, the method comprising the steps of: (a) contacting a sample from the mammal derived from the mammal with a binding moiety that binds specifically to a protein comprising an amino acid sequence of SEQ ID NO:5, thereby to produce a complex; and (b) determining whether the complex is present in an amount greater than or equal to a threshold value indicative of the presence of breast cancer in the mammal, wherein an amount greater than or equal to the threshold value is indicative of the presence of breast cancer in the mammal and an amount less than the threshold value is indicative of the absence of breast cancer in the mammal.

8. The method of claim 6 or 7, wherein the binding moiety is selected from the group consisting of an antibody, an antibody fragment and a **biosynthetic antibody binding site.**

9. The method of claim 6 or 7, wherein the binding moiety is an antibody.

10. The method of claim 9, wherein,the antibody is a monoclonal antibody.

11. The method of claim 8, wherein the binding moiety is labeled with a detectable moiety.

12. The method of claim 6, wherein the absence of a detectable amount of the complex is indicative of the absence of breast cancer.

13. The method of claim 4, wherein the body fluid is serum.

14. The method of claim 6 or 7, wherein the sample comprises breast tissue.

15. The method of claim 6 or 7, wherein the sample comprises a body fluid.

16. The method of claim 15, wherein the body fluid is selected from the group consisting of blood, serum, plasma, sweat, tears, urine,

peritoneal fluid, lymph, vaginal secretions, semen, spinal fluid, ascitic fluid, saliva, sputum, and breast exudate.

17. The method of claim 15, wherein the body fluid is serum.

18. The method of claim 1, wherein the presence of a detectable amount of the protein is indicative of the presence of breast cancer in the mammal.

19. The method of claim 1, wherein the absence of a detectable amount of the protein is indicative of the absence of breast cancer in the mammal.

L22 ANSWER 4 OF 15 USPATFULL on STN
2003:264820 Methods and compositions for treating conditions of the eye.
Miller, Joan W., Winchester, MA, UNITED STATES
Gragoudas, Evangelos S., Lexington, MA, UNITED STATES
Renno, Reem Z., Boston, MA, UNITED STATES
US 2003185834 A1 20031002
APPLICATION: US 2003-429428 A1 20030505 (10)
PRIORITY: US 2000-181641P 20000210 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of treating unwanted choroidal neovasculature in a mammal, the choroidal neovasculature comprising endothelial cells, the method comprising the steps of: (a) administering to the mammal an anti-angiogenesis factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature; (b) administering to the mammal an amount of photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature; and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, wherein damage to the endothelial cells resulting from steps (a), (b), and (c) is greater than that resulting only from steps (b) and (c).

2. The method of claim 1, wherein the mammal is a primate.

3. The method of claim 2, wherein the primate is a human.

4. The method of claim 1, wherein the anti-angiogenesis factor is administered to the mammal prior to administration of the photosensitizer.

5. The method of claim 1, wherein the photosensitizer is an amino acid derivatives, an azo dye, a xanthene derivative, a chlorin, a tetrapyrrole derivative, or a phthalocyanine.

6. The method of claim 5, wherein the photosensitizer is lutetium texaphyrin, a benzoporphyrin, a benzoporphyrin derivative, a hematoporphyrin, or a hematoporphyrin derivative.

7. The method of claim 1, wherein the anti-angiogenesis factor is angiostatin, endostatin, a peptide containing a RGD tripeptide sequence and capable of binding the αvB3 integrin, a COX-2 inhibitor or pigment epithelium derived growth factor.

8. The method of claim 1, wherein occlusion of the choroidal neovasculature resulting from steps (a), (b) and (c) is greater than that resulting from steps (b) and (c) alone.

9. The method of claim 1, wherein the method more selectively occludes choroidal neovasculature relative to the same treatment lacking administration of the anti-angiogenesis factor.

10. A method of treating unwanted choroidal neovasculature in a mammal, the choroidal neovasculature comprising endothelial cells, the method comprising the steps of: (a) administering to the mammal an amount of photosensitizer to permit an effective amount to localize in the neovasculature, the photosensitizer comprising a targeting moiety that binds preferentially to endothelial cells of the neovasculature; and (b) irradiating the neovasculature with a laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature.

11. The method of claim 10, wherein the mammal is a primate.

12. The method of claim 11, wherein the mammal is a human.

13. The method of claim 10, wherein the targeting moiety is a peptide.

14. The method of claim 13, wherein the peptide binds specifically to an α-v β integrin or is an antibody that binds specifically to a vascular endothelial growth factor receptor.

15. The method of claim 14, wherein the integrin is α-v β3 integrin or α-v β5 integrin.

16. The method of claim 14, wherein the antibody is a monoclonal antibody or an antigen binding fragment thereof, a polyclonal antibody or an antigen binding fragment thereof, or a **biosynthetic antibody binding site**.

17. The method of claim 10, wherein the photosensitizer is an amino acid derivatives, an azo dye, a xanthene derivative, a chlorin, a tetrapyrrole derivative, and a phthalocyanine.

18. The method of claim 17, wherein the photosensitizer is lutetium texaphryin, a benzoporphyrin, a benzoporphyrin derivative, a hematoporphyrin or a hematoporphyrin derivative.

19. The method of claim 10, wherein the targeting moiety enhances the specificity of the photosensitizer to choroidal neovasculature relative to photosensitizer lacking the targeting moiety.

20. A method of treating unwanted choroidal neovasculature in a mammal, the method comprising the steps of: (a) administering to the mammal, an apoptosis-modulating factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature or tissue surrounding the choroidal neovasculature; (b) administering to the mammal an amount of photosensitizer sufficient to permit an effective amount of localize in the choroidal neovasculature; and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, wherein the level of cell damage to the choroidal neovasculature relative to the tissue surrounding the choroidal neovasculature resulting from steps (a), (b) and (c) is greater than that resulting from steps (b) and (c) alone.

21. The method of claim 20, wherein the mammal is a primate.

22. The method of claim 21, wherein the mammal is a human.

23. The method of claim 20, wherein the factor is administered to the primate before administration of the photosensitizer.

24. The method of claim 20, wherein the photosensitizer is an amino acid derivatives, an azo dye, a xanthene derivative, a chlorin, a tetrapyrrole derivative, or a phthalocyanine.

25. The method of claim 20, wherein the photosensitizer is lutetium texaphyrin, a benzoporphyrin, a benzoporphyrin derivative, a hematoporphyrin or a hematoporphyrin derivative.

26. The method of claim 20, wherein the apoptosis modulating factor induces or represses apoptosis.

27. The method of claim 26, wherein the factor is a peptide.

28. The method of claim 27, wherein the peptide selectively binds to neovasculature.

29. The method of claim 27, wherein the peptide induces apoptosis in endothelial cells.

30. The method of claim 29, wherein the peptide comprises an amino acid sequence comprising, in an N- to C-terminal direction, KLAKLAKKLAKLAK (SEQ. ID. NO 1).

31. The method of claim 30, wherein the peptide further comprises an RGD-4C peptide sequence.

32. The method of claim 1, wherein the method ameliorates the symptoms of a disorder selected from the group consisting of age-related macular degeneration, ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, idiopathic disorders, choroiditis, choroidal rupture, overlying choroid nevi, and inflammatory diseases.

L22 ANSWER 5 OF 15 USPATFULL on STN
2003:250497 Methods and compositions for treating conditions of the eye.
Miller, Joan W., Winchester, MA, UNITED STATES
Gragoudas, Evangelos S., Lexington, MA, UNITED STATES
Renno, Reem Z., Boston, MA, UNITED STATES
US 2003175282 A1 20030918
APPLICATION: US 2003-429496 A1 20030505 (10)
PRIORITY: US 2000-181641P 20000210 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of treating unwanted choroidal neovasculature in a mammal, the choroidal neovasculature comprising endothelial cells, the method comprising the steps of: (a) administering to the mammal an anti-angiogenesis factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature; (b) administering to the mammal an amount of photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature; and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, wherein damage to the endothelial cells resulting from steps (a), (b), and (c) is greater than that resulting only from steps (b) and (c).

2. The method of claim 1, wherein the mammal is a primate.

3. The method of claim 2, wherein the primate is a human.

4. The method of claim 1, wherein the anti-angiogenesis factor is administered to the mammal prior to administration of the photosensitizer.

5. The method of claim 1, wherein the photosensitizer is an amino acid derivatives, an azo dye, a xanthene derivative, a chlorin, a tetrapyrrole derivative, or a phthalocyanine.

6. The method of claim 5, wherein the photosensitizer is lutetium texaphyrin, a benzoporphyrin, a benzoporphyrin derivative, a hematoporphyrin, or a hematoporphyrin derivative.

7. The method of claim 1, wherein the anti-angiogenesis factor is angiostatin, endostatin, a peptide containing a RGD tripeptide sequence and capable of binding the αvB3 integrin, a COX-2 inhibitor or pigment epithelium derived growth factor.

8. The method of claim 1, wherein occlusion of the choroidal neovasculature resulting from steps (a), (b) and (c) is greater than that resulting from steps (b) and (c) alone.

9. The method of claim 1, wherein the method more selectively occludes choroidal neovasculature relative to the same treatment lacking administration of the anti-angiogenesis factor.

10. A method of treating unwanted choroidal neovasculature in a mammal, the choroidal neovasculature comprising endothelial cells, the method comprising the steps of: (a) administering to the mammal an amount of photosensitizer to permit an effective amount to localize in the neovasculature, the photosensitizer comprising a targeting moiety that binds preferentially to endothelial cells of the neovasculature; and (b) irradiating the neovasculature with a laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature.

11. The method of claim 10, wherein the mammal is a primate.

12. The method of claim 11, wherein the mammal is a human.

13. The method of claim 10, wherein the targeting moiety is a peptide.

14. The method of claim 13, wherein the peptide binds specifically to an α-vβ integrin or is an antibody that binds specifically to a vascular endothelial growth factor receptor.

15. The method of claim 14, wherein the integrin is α-vβ3 integrin or α-vβ5 integrin.

16. The method of claim 14, wherein the antibody is a monoclonal antibody or an antigen binding fragment thereof, a polyclonal antibody or an antigen binding fragment thereof, or a **biosynthetic antibody binding site**.

17. The method of claim 10, wherein the photosensitizer is an amino acid derivatives, an azo dye, a xanthene derivative, a chlorin, a tetrapyrrole derivative, and a phthalocyanine.

18. The method of claim 17, wherein the photosensitizer is lutetium texaphryin, a benzoporphyrin, a benzoporphyrin derivative, a hematoporphyrin or a hematoporphyrin derivative.

19. The method of claim 10, wherein the targeting moiety enhances the specificity of the photosensitizer to choroidal neovasculature relative to photosensitizer lacking the targeting moiety.

20. A method of treating unwanted choroidal neovasculature in a mammal, the method comprising the steps of: (a) administering to the mammal, an apoptosis-modulating factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature or tissue surrounding the choroidal neovasculature; (b) administering to the mammal an amount of photosensitizer sufficient to permit an effective amount of localize in the choroidal neovasculature; and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, wherein the level of cell damage to the choroidal neovasculature relative to the tissue surrounding the choroidal neovasculature resulting from steps (a), (b) and (c) is greater than that resulting from steps (b) and (c) alone.

21. The method of claim 20, wherein the mammal is a primate.

22. The method of claim 21, wherein the mammal is a human.

23. The method of claim 20, wherein the factor is administered to the primate before administration of the photosensitizer.

24. The method of claim 20, wherein the photosensitizer is an amino acid derivatives, an azo dye, a xanthene derivative, a chlorin, a tetrapyrrole derivative, or a phthalocyanine.

25. The method of claim 20, wherein the photosensitizer is lutetium texaphyrin, a benzoporphyrin, a benzoporphyrin derivative, a hematoporphyrin or a hematoporphyrin derivative.

26. The method of claim 20, wherein the apoptosis modulating factor induces or represses apoptosis.

27. The method of claim 26, wherein the factor is a peptide.

28. The method of claim 27, wherein the peptide selectively binds to neovasculature.

29. The method of claim 27, wherein the peptide induces apoptosis in endothelial cells.

30. The method of claim 29, wherein the peptide comprises an amino acid sequence comprising, in an N- to C-terminal direction, KLAKLAKKLAKLAK (SEQ. ID. NO 1).

31. The method of claim 30, wherein the peptide further comprises an RGD-4C peptide sequence.

32. The method of claim 1, wherein the method ameliorates the symptoms of a disorder selected from the group consisting of age-related macular degeneration, ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, idiopathic disorders, choroiditis, choroidal rupture, overlying choroid nevi, and inflammatory diseases.

L22 ANSWER 6 OF 15 USPATFULL on STN
2003:109700 Shape information coding and decoding apparatus for adaptively bordering and method therefor.

Chun, Sung-Moon, Kyoungki-do, KOREA, REPUBLIC OF
Shin, Dong-Kyoo, Seoul, KOREA, REPUBLIC OF
Moon, Joo-Hee, Seoul, KOREA, REPUBLIC OF
Hyundai Electronics Ind. Co., LTD, Kyoungki-do, KOREA, REPUBLIC OF
(non-U.S. corporation)
US 6553149 B1 20030422
APPLICATION: US 1998-173883 19981016 (9)
PRIORITY: KR 1997-53477 19971017
DOCUMENT TYPE: Utility; GRANTED.

CLM What is claimed is:

1. In a shape information coding apparatus for determining a mode based upon characteristics of a binary alpha block (BAB) adaptively performing a field bordering, and coding said shape information by field mode bordering and coding means, when a field type is determined as said coding mode, said field mode bordering and coding means comprising: current BAB memory means for receiving said shape information and storing a current BAB; neighborhood BAB memory means for receiving said shape information and storing **BABs** neighboring with said current BAB; top border generating means for reading pixels within a bordering size in a BAB which neighbors with a top of said current BAB stored in said neighborhood BAB memory means and storing them; left border generating means for reading pixels within a bordering size at a most right side in a BAB which neighbors with a left side of said current BAB stored in said neighborhood BAB memory means and storing them; left top border generating means for reading pixels within a bordering size at a most right bottom side in a BAB which neighbors with a left top side of said current BAB stored in said neighborhood BAB memory means and storing them; right top border generating means for reading pixels within a bordering size at a most left bottom side in a BAB which neighbors with a right top side of said current BAB stored in said neighborhood BAB memory means and storing them; multiple top field border generating means for reading top field borders from said multiple border generating means and storing them; multiple bottom field border generating means for reading bottom field borders from said multiple border generating means and storing them; top field bordering means for reading said top field borders from said multiple top field border generating means and constructing a bordered top field BAB; and bottom field bordering means for reading said bottom field borders from said multiple bottom field border generating means and constructing a bordered bottom field BAB.

2. The apparatus according to claim 1, wherein said left border generating means performs the bordering in M×1 size; said top border generating means, in 2i×N size; and said left top and right top border generating means, in 2i×i size, wherein "M" is a length of said BAB, "N" is a breadth of said BAB, and "i" is a width of the border.

3. The apparatus according to claim 1, wherein said left border generating means reads pixels within the bordering size of M/2×i and stores them; said top and bottom border generating means reads pixels within the bordering size of 2i×N and store them; and said left top and right top border generating means read pixels within the bordering size of 2i×i and store them; wherein "M" is a length of said BAB, "N" is a breadth of said BAB, and "i" is a width of the border.

L22 ANSWER 7 OF 15 USPATFULL on STN
2002:294621 Detection and treatment of prostate cancer.
Hlavaty, John J., Beverly, MA, UNITED STATES
Briggman, Joseph V., Westford, MA, UNITED STATES
Matritech, Inc. (U.S. corporation)

US 2002164664 A1 20021107
APPLICATION: US 2001-998909 A1 20011130 (9)
PRIORITY: US 2000-250284P 20001130 (60)
US 2001-344948P 20011108 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of diagnosing prostate cancer in an individual comprising: detecting in a sample isolated from the individual the presence of a polypeptide comprising an amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:1; the sequence of SEQ ID NO:2; the sequence of SEQ ID NO:3; the sequence of SEQ ID NO:5; the sequence of SEQ ID NO:6; the sequence of SEQ ID NO:7; the sequence of SEQ ID NO:8; the sequence of SEQ ID NO:9; the sequence of SEQ ID NO:10; the sequence of SEQ ID NO:11; and a sequence comprising SEQ ID NO:4 and SEQ ID NO:12, wherein the presence of the polypeptide is indicative of prostate cancer in the individual.

2. The method of claim 1, wherein the polypeptide is present in samples from more than fifty percent of males with prostate cancer and absent in samples from more than fifty percent of males without prostate cancer.

3. The method of claim 1, wherein the sample comprises prostate tissue.

4. The method of claim 1, wherein the sample comprises a body fluid.

5. The method of claim 4, wherein the body fluid is selected from the group consisting of blood, serum, plasma, sweat, tears, urine, peritoneal fluid, lymph, semen, seminal fluid, seminal plasma, prostatic secretion, spinal fluid, ascitic fluid, saliva, and sputum.

6. The method of claim 5, wherein the body fluid is serum, plasma, or prostatic secretion.

7. The method of claim 1, further comprising the step of measuring the concentration of the polypeptide in the sample.

8. The method of claim 7, further comprising the step of comparing the concentration of the polypeptide with a threshold value, wherein a concentration of the polypeptide greater than or equal to the threshold value is indicative of the presence of prostate cancer.

9. The method of claim 1, wherein the polypeptide is detected by mass spectrometry.

10. A method of diagnosing prostate cancer in an individual, the method comprising the steps of: (a) contacting a sample from the individual with a binding moiety that binds specifically to a cancer-associated protein to produce a binding moiety-cancer-associated protein complex, the cancer-associated protein comprising an amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:1; the sequence of SEQ ID NO:2; the sequence of SEQ ID NO:3; the sequence of SEQ ID NO:5; the sequence of SEQ ID NO:6; the sequence of SEQ ID NO:7; the sequence of SEQ ID NO:8; the sequence of SEQ ID NO:9; the sequence of SEQ ID NO:10; the sequence of SEQ ID NO:11, and a sequence comprising SEQ ID NO:4 and SEQ ID NO:12; and (b) detecting the complex, which if present is indicative of prostate cancer in the individual.

11. The method of claim 10, wherein the binding moiety is an antibody.

12. The method of claim 11, wherein the antibody is a monoclonal antibody.

13. The method of claim 11, wherein the antibody is a polyclonal antibody.

14. The method of claim 11, wherein the antibody is labeled with a detectable moiety.

15. The method of claim 14, wherein the detectable moiety comprises a member selected from the group consisting of a radioactive label, a hapten label, a fluorescent label, a chemiluminescent label, a spin label, a colored label, and an enzymatic label.

16. A composition comprising: an isolated polypeptide that (a) binds to an anion exchange resin comprising quarternary ammonium groups in the presence of a first solution consisting essentially of 50 mM sodium phosphate, pH 7.0, (b) elutes from the anion exchange resin in the presence of a second solution consisting essentially of 125 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, after the resin has been washed with a solution consisting essentially of 25 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, a solution consisting essentially of 50 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, and a solution consisting essentially of 75 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, and (c) comprises an amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:1; the sequence of SEQ ID NO:2; the sequence of SEQ ID NO:3; the sequence of SEQ ID NO:5; the sequence of SEQ ID NO:6; the sequence of SEQ ID NO:7; the sequence of SEQ ID NO:8; the sequence of SEQ ID NO:9; the sequence of SEQ ID NO:10; the sequence of SEQ ID NO:11, and a sequence comprising SEQ ID NO:4 and SEQ ID NO:12.

17. The polypeptide of claim 14, wherein the polypeptide has a mass of about 50.8 kD as measured by MALDI-TOF mass spectrometry using a derivatized chip surface.

18. The polypeptide of claim 14, wherein the polypeptide has an affinity for a derivatized, weak cationic exchange chip surface comprising carboxyl groups or for a derivatized chip surface comprising nickel ions.

19. A composition comprising: an isolated polypeptide that (a) binds to an anion exchange resin comprising quarternary ammonium groups in the presence of a first solution consisting essentially of 50 mM sodium phosphate, pH 7.0, (b) elutes from the anion exchange resin in the presence of a second solution consisting essentially of 125 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, after the resin has been washed with a solution consisting essentially of 25 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, a solution consisting essentially of 50 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, and a solution consisting essentially of 75 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, and (c) binds specifically to an anti-VDBP antibody.

20. A method of diagnosing cancer in an individual comprising: detecting in a sample isolated from the individual a polypeptide that (a) binds to an anion exchange resin comprising quarternary ammonium groups in the presence of a first solution consisting essentially of 50 mM sodium phosphate, pH 7.0, (b) elutes from the anion exchange resin in the presence of a second solution consisting essentially of 125 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, after the resin has been washed with a solution consisting essentially of 25 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, a solution consisting essentially of 50 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, and a solution consisting essentially of 75 mM sodium chloride in 50 mM

sodium phosphate, pH 7.0, and (c) comprises an amino acid sequence selected from the group consisting of the sequence of SEQ ID NO:1; the sequence of SEQ ID NO:2; the sequence of SEQ ID NO:3; the sequence of SEQ ID NO:5; the sequence of SEQ ID NO:6; the sequence of SEQ ID NO:7; the sequence of SEQ ID NO:8; the sequence of SEQ ID NO:9; the sequence of SEQ ID NO:10; the sequence of SEQ ID NO:11, and a sequence comprising SEQ ID NO:4 and SEQ ID NO:12, wherein presence of the polypeptide is indicative of cancer in the individual.

21. The method of claim 20, wherein the cancer is prostate cancer.

22. The method of claim 20, wherein the sample comprises prostate tissue.

23. The method of claim 20, wherein the sample comprises a body fluid.

24. The method of claim 23, wherein the body fluid is selected from the group consisting of blood, serum, plasma, sweat, tears, urine, peritoneal fluid, lymph, semen, seminal fluid, seminal plasma, prostatic secretion, spinal fluid, ascitic fluid, saliva, and sputum.

25. The method of claim 24, wherein the body fluid is serum plasma or prostatic secretion.

26. The method of claim 24, further comprising the step of measuring the concentration of the polypeptide in the sample.

27. The method of claim 26, further comprising the step of comparing the concentration of the polypeptide with a threshold value, wherein a concentration of the polypeptide greater than or equal to the threshold value is indicative of the presence of cancer.

28. The method of claim 24, wherein the polypeptide is detected by mass spectrometry.

29. A method of diagnosing cancer in an individual, the method comprising the steps of: (a) contacting a sample from the individual with a binding moiety that binds specifically to a cancer-associated protein to produce a binding moiety-cancer-associated protein complex, wherein the binding moiety binds specifically to a polypeptide as in any one of claims 16-19; and (b) detecting the presence of the complex, which if present is indicative of the presence of cancer in the individual.

30. The method of claim 29, wherein the binding moiety is an antibody.

31. The method of claim 30, wherein the antibody is a monoclonal antibody.

32. The method of claim 30, wherein the antibody is a polyclonal antibody.

33. The method of claim 30, wherein the antibody is labeled with a detectable moiety.

34. The method of claim 33, wherein the detectable moiety comprises a member selected from the group consisting of a radioactive label, a hapten label, a fluorescent label, a chemiluminescent label, a spin label, a colored label, and an enzymatic label.

35. The method of claim 10, wherein the polypeptide is present in samples from more than fifty percent of males with prostate cancer and

absent in samples from more than fifty percent of males without prostate cancer.

36. The method of claim 20, wherein the polypeptide is present in samples from more than fifty percent of males with prostate cancer and absent in samples from more than fifty percent of males without prostate cancer.

37. The method of claim 29, wherein the polypeptide is present in samples from more than fifty percent of males with prostate cancer and absent in samples from more than fifty percent of males without prostate cancer.

38. A kit for detecting cancer or for evaluating the efficacy of a therapeutic treatment for cancer, the kit comprising in combination: a receptacle for receiving a tissue or body fluid sample from a mammal; a binding moiety which binds specifically to a polypeptide as in any one of claims 16-19; and a reference sample.

39. The kit of claim 35, wherein the reference sample is indicative of an individual without prostate cancer.

40. An isolated, prostate cancer-associated polypeptide, said polypeptide comprising the characteristics of: detectable at a higher concentration in serum of a human with prostate cancer than in serum of a human without prostate cancer; and (i) has a molecular weight of about 21 kD as measured by MALDI-TOF mass spectrometry using a derivatized chip surface, binds to an anion ion exchange resin in the presence of a first solution consisting essentially of 50 mM sodium phosphate, pH 7.0, and elutes from the ion exchange resin in the presence of a second solution consisting essentially of 125 mM sodium chloride in 50 mM to sodium phosphate, pH 7.0; (ii) has a molecular weight of about 23 kD as measured by MALDI-TOF mass spectrometry using a derivatized chip surface, binds to an anion exchange resin in the presence of a first solution consisting essentially of 50 mM sodium phosphate, pH 7.0, and elutes from the anion ion exchange resin in the presence of a second solution consisting essentially of 175 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, (iii) has a molecular weight of about 25 kD as measured by MALDI-TOF mass spectrometry using a derivatized chip surface, binds to an anion exchange resin in the presence of a first solution consisting essentially of 50 mM sodium phosphate, pH 7.0, and elutes from the ion exchange resin in the presence of a second solution consisting essentially of 125 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, (iv) has a molecular weight of about 26 kD as measured by MALDI-TOF mass spectrometry using a derivatized chip surface, binds to an anion exchange resin in the presence of a first solution consisting essentially of 50 mM sodium phosphate, pH 7, and elutes from the ion exchange resin in the presence of a second solution consisting essentially of 100 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, (v) has a molecular weight of about 51 kD as measured by MALDI-TOF mass spectrometry using a derivatized chip surface, binds to an anion exchange resin in the presence of a first solution consisting essentially of 50 mM sodium phosphate, pH 7.0, elutes from an ion exchange resin in the presence of a second solution consisting essentially of 125 mM sodium chloride in 50 mM sodium phosphate, pH 7.0, and has an affinity for a derivatized chip surface bearing nickel ions, (vi) has a molecular weight of about 60 kD as measured by MALDI-TOF mass spectrometry using a derivatized chip surface and weakly binds an anion exchange resin in the presence of a solution consisting essentially of 50 mM sodium phosphate, pH 7.0, or (vii) has a molecular weight of about 125 kD as measured by MALDI-TOF mass spectrometry using a derivatized chip surface, binds to an anion

exchange resin in the presence of a first solution consisting essentially of 50 mM sodium phosphate, pH 7.0, and elutes from an ion exchange resin in the presence of a second solution consisting essentially of 125 mM sodium chloride in 50 mM sodium phosphate, pH 7.0.

41. The polypeptide of claim 40, wherein the polypeptide of clause (i), or (iv) is further characterized as having an affinity to an chip surface derivatized to comprise hydrophobic moieties.

42. The polypeptide of claim 40, wherein the polypeptide of clause (iii) is further characterized as having an affinity to a chip surface derivatized to comprise carboxyl moieties.

43. The polypeptide of claim 40, wherein the polypeptide of clause (ii), (vi), or (vii) is further characterized as having an affinity to a chip surface derivatized to comprise nickel ions.

44. The polypeptide of claim 40, wherein the prostate cancer is organ-confined prostate cancer.

45. The polypeptide of claim 40, comprising the additional characteristic of being a non-immunoglobulin protein.

46. The polypeptide of claim 40, comprising the additional characteristic of being a non-albumin protein.

47. The polypeptide of claim 40, further comprising an epitope.

48. A method of diagnosing cancer in an individual comprising detecting in a sample isolated from the individual the presence of the polypeptide of claim 40, which if present is indicative of cancer in the individual.

49. The method of claim 48, wherein the cancer is prostate cancer.

50. The method of claim 48, wherein the sample comprises prostate tissue.

51. The method of claim 48, wherein the sample comprises a body fluid.

52. The method of claim 51, wherein the body fluid is selected from the group consisting of blood, serum, plasma, sweat, tears, urine, peritoneal fluid, lymph, semen, seminal fluid, seminal plasma, prostatic secretion, spinal fluid, ascitic fluid, saliva, and sputum.

53. The method of claim 52, wherein the body fluid is serum plasma, or prostatic secretion.

54. A method of diagnosing cancer in an individual, the method comprising the steps of: (c) contacting a sample from the individual with a binding moiety that binds specifically to a cancer-associated protein to produce a binding moiety-cancer-associated protein complex, wherein the binding moiety binds specifically to the polypeptide of claim 40; and (d) detecting the presence of the complex, which if present is indicative of the presence of cancer in the individual.

55. The method of claim 54, wherein the binding moiety is an antibody.

56. The method of claim 55, wherein the antibody is a monoclonal antibody.

57. The method of claim 55, wherein the antibody is a polyclonal antibody.

58. The method of claim 55, wherein the antibody is labeled with a detectable moiety.

59. The method of claim 58, wherein the detectable moiety comprises a member selected from the group consisting of a radioactive label, a hapten label, a fluorescent label, a chemiluminescent label, a spin label, a colored label, and an enzymatic label.

60. An isolated binding moiety that binds specifically the polypeptide of claim 40.

61. The binding moiety of claim 60, wherein the moiety is an antibody, an antigen-binding fragment thereof or a **biosynthetic antibody binding site**.

62. The binding moiety of claim 60, wherein the binding moiety is a monoclonal antibody.

63. A pharmaceutical composition comprising the binding moiety of claim 60 in a pharmaceutically-acceptable carrier.

64. A method of treating cancer in an individual, the method comprising administering to the individual a therapeutically-effective amount of the composition of claim 63.

65. The method of claim 64, wherein the cancer is prostate cancer.

66. An isolated nucleic acid sequence encoding the protein according to any of claims 16-19 or claim 40, or a sequence complementary thereto.

67. An isolated nucleic acid sequence comprising at least 15 nucleotides and capable of hybridizing under stringent hybridization conditions to the nucleic acid of claim 66.

68. An expression vector comprising the nucleic acid of claim 67.

69. A composition comprising the nucleic acid of claim 67 admixed with a pharmaceutically acceptable carrier.

70. A composition comprising the nucleic acid of claim 68 admixed with a pharmaceutically acceptable carrier.

71. A method of treating cancer in an individual, the method comprising introducing into cells of the individual the expression vector of claim 68.

72. The method of claim 71, wherein the cancer is prostate cancer.

73. A method of detecting the presence of prostate cancer in a human, the method comprising detecting the presence of a nucleic acid molecule in a tissue or body fluid sample of the human thereby to indicate the presence of prostate cancer in the human, wherein the nucleic acid molecule comprises a nucleic acid sequence encoding at least a portion of a prostate cancer-associated protein according to any of claims 16-19 or claim 40, or a nucleic acid sequence capable of recognizing and being specifically bound by the prostate cancer-associated protein.

74. The method of claim 73, wherein the method comprises the step of reacting the sample with a labeled hybridization probe capable of hybridizing specifically to the nucleic acid molecule.

75. A method of detecting the presence of cancer in an individual, the method comprising the steps of: (a) exposing a sample from the individual under specific hybridization conditions to a nucleic acid probe capable of hybridizing specifically to a target nucleic acid encoding a polypeptide according to any of claims 16-19 or claim 40; and (b) detecting the presence of a duplex comprising the nucleic acid probe, the presence of the duplex being indicative of cancer in the individual.

76. The method of claim 75 further comprising the step of amplifying the target nucleic acid in the sample prior to exposing the sample to the nucleic acid probe.

77. The method of claim 75, wherein the cancer is prostate cancer.

78. The method of claim 75, wherein the nucleic acid probe is labeled with a detectable moiety.

79. The method of claim 78, wherein the detectable moiety comprises a member selected from the group consisting of a radioactive label, a hapten label, a fluorescent label, and an enzymatic label.

80. A kit for detecting the presence of prostate cancer or for evaluating the efficacy of a therapeutic treatment of a prostate cancer, the kit comprising in combination: a receptacle for receiving a tissue or body fluid sample from a mammal; a binding moiety which binds specifically to the prostate cancer-associated protein of claim 40; and a reference sample.

81. The kit of claim 80, wherein the reference sample is indicative of an individual without prostate cancer.

L22 ANSWER 8 OF 15 USPATFULL on STN
2002:280588 Immunostimulatory nucleic acids and cancer medicament combination therapy for the treatment of cancer.
Bratzler, Robert L., Concord, MA, UNITED STATES
Petersen, Deanna M., Newton, MA, UNITED STATES
US 2002156033 A1 20021024
APPLICATION: US 2001-800266 A1 20010305 (9)
PRIORITY: US 2000-187214P 20000303 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for treating a subject having, or at risk of developing, a cancer, comprising: administering to a subject in need of such treatment a poly-G nucleic acid and a cancer medicament in an effective amount to treat the cancer or to reduce the risk of developing the cancer, wherein the poly-G nucleic acid is not conjugated to the cancer medicament.

2. The method of claim 1, wherein the cancer medicament is selected from the group consisting of a chemotherapeutic agent, an immunotherapeutic agent, and a cancer vaccine.

3. The method of claim 2, wherein the chemotherapeutic agent is selected from the group consisting of methotrexate, vincristine, adriamycin, cisplatin, non-sugar containing chloroethylnitrosoureas, 5-fluorouracil, mitomycin C, bleomycin, doxorubicin, dacarbazine, taxol, fragyline, Meglamine GLA, valrubicin, carmustaine and poliferposan, MM1270, BAY 12-9566, RAS famesyl transferase inhibitor, famesyl transferase inhibitor, MMP, MTA/LY231514, LY264618/Lometexol, Glamolec, CI-994,

TNP-470, Hycamtin/Topotecan, PKC412, Valspodar/PSC833, Novantrone/Mitroxantrone, Metaret/Suramin, Batimastat, E7070, BCH-4556, CS-682, 9-AC, AG3340, AG3433, Incel/VX-710, VX-853, ZD0101, ISI641, ODN 698, TA 2516/Marmistat, BB2516/Marmistat, CDP 845, D2163, PD183805, DX8951f, Lemonal DP 2202, FK 317, Picibanil/OK-432, AD 32/Valrubicin, Metastron/strontium derivative, Temodal/Temozolomide, Evacet/liposomal doxorubicin, Yewtaxan/Placlitaxel, Taxol/Paclitaxel, Xeload/Capecitabine, Furtulon/Doxifluridine, Cyclopax/oral paclitaxel, Oral Taxoid, SPU-077/Cisplatin, HMR 1275/Flavopiridol, CP-358 (774)/EGFR, CP-609 (754)/RAS oncogene inhibitor, BMS-182751/oral platinum, UFT(Tegafur/Uracil), Ergamisol/Levamisole, Eniluracil/776C85/5FU enhancer, Campto/Levamisole, Camptosar/Irinotecan, Tumodex/Ralitrexed, Leustatin/Cladribine, Paxex/Paclitaxel, Doxil/liposomal doxorubicin, Caelyx/liposomal doxorubicin, Fludara/Fludarabine, Pharmarubicin/Epirubicin, DepoCyt, ZD1839, LU 79553/Bis-Naphtalimide, LU 103793/Dolastain, Caetyx/liposomal doxorubicin, Gemzar/Gemcitabine, ZD 0473/Anormed, YM 116, Iodine seeds, CDK4 and CDK2 inhibitors, PARP inhibitors, D4809/Dexifosamide, Ifes/Mesnex/Ifosamide, Vumon/Teniposide, Paraplatin/Carboplatin, Plantinol/cisplatin, Vepeside/Etoposide, ZD 9331, Taxotere/Docetaxel, prodrug of guanine arabinoside, Taxane Analog, nitrosoureas, alkylating agents such as melphelan and cyclophosphamide, Aminoglutethimide, Asparaginase, Busulfan, Carboplatin, Chlorombucil, Cytarabine HCl, Dactinomycin, Daunorubicin HCl, Estramustine phosphate sodium, Etoposide (VP16-213), Floxuridine, Fluorouracil (5-FU), Flutamide, Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alfa-2a, Alfa-2b, Leuprolide acetate (LHRH-releasing factor analogue), Lomustine (CCNU), Mechlorethamine HCl (nitrogen mustard), Mercaptopurine, Mesna, Mitotane (o.p'-DDD), Mitoxantrone HCl, Octreotide, Plicamycin, Procarbazine HCl, Streptozocin, Tamoxifen citrate, Thioguanine, Thiotepa, Vinblastine sulfate, Amsacrine (m-AMSA), Azacitidine, Erthropoietin, Hexamethylmelamine (HMM), Interleukin 2, Mitoguazone (methyl-GAG; methyl glyoxal bis-guanylhydrazone; MGBG), Pentostatin (2'deoxycoformycin), Semustine (methyl-CCNU), Teniposide (VM-26) and Vindesine sulfate.

4. The method of claim 2, wherein the immunotherapeutic agent is selected from the group consisting of Ributaxin, Herceptin, Quadramet, Panorex, IDEC-Y2B8, BEC2, C225, Oncolym, SMART M1 95, ATRAGEN, Ovarex, Bexxar, LDP-03, ior t6, MDX-210, MDX-11, MDX-22, OV103, 3622W94, anti-VEGF, Zenapax, MDX-220, MDX-447, MELIMMUNE-2, MELIMMUNE-1, CEACIDE, Pretarget, NovoMAb-G2, TNT, Gliomab-H, GNI-250, EMD-72000, LymphoCide, CMA 676, Monopharm-C, 4B5, ior egf.r3, ior c5, BABS, anti-FLK-2, MDX-260, ANA Ab, SMART 1D10 Ab, SMART ABL 364 Ab and ImmuRAIT-CEA.

5. The method of claim 2, wherein the cancer vaccine is selected from the group consisting of EGF, Anti-idiotypic cancer vaccines, Gp75 antigen, GMK melanoma vaccine, MGV ganglioside conjugate vaccine, Her2/neu, Ovarex, M-Vax, O-Vax, L-Vax, STn-KHL theratope, BLP25 (MUC-1), liposomal idiotypic vaccine, Melacine, peptide antigen vaccines, toxin/antigen vaccines, MVA-based vaccine, PACIS, BCG vacine, TA-HPV, TA-CIN, DISC-virus and ImmuCyst/TheraCys.

6. The method of claim 1, wherein the cancer medicament is a hormone therapy.

7. The method of claim 1, wherein the cancer medicament is taxol.

8. The method of claim 1, further comprising administering interferon-α to the subject.

9. The method of claim 1, wherein the cancer is selected from the group consisting of bone cancer, brain and CNS cancer, connective tissue

cancer, esophageal cancer, eye cancer, Hodgkin's lymphoma, larynx cancer, oral cavity cancer, skin cancer, and testicular cancer.

10. The method of claim 1, wherein the immunostimulatory nucleic acid has a modified backbone.

11. The method of claim 10, wherein the modified backbone is a phosphorothioate modified backbone.

12. A method for treating a subject having or at risk of developing a cancer, comprising: administering to a subject in need of such treatment, an immunostimulatory nucleic acid having a modified backbone and a cancer medicament selected from the group consisting of an immunotherapeutic agent, a cancer vaccine and a hormone therapy, wherein the immunostimulatory nucleic acid is free of a CpG motif, and a T-rich motif.

13. The method of claim 12, wherein the immunostimulatory nucleic acid is a poly-G nucleic acid.

14. The method of claim 13, wherein the poly-G nucleic acid is not conjugated to the cancer medicament.

15. The method of claim 12, wherein the cancer medicament is taxol.

16. The method of claim 12, further comprising administering interferon-α to the subject.

17. The method of claim 12, further comprising administering a cancer antigen to the subject.

18. The method of claim 17, wherein the cancer antigen is not conjugated to the immunostimulatory nucleic acid.

19. The method of claim 12, wherein the immunostimulatory nucleic acid has a nucleotide sequence selected from the group consisting of SEQ ID NO:134 through to SEQ. ID NO:146.

20. The method of claim F3, wherein the modified backbone is a phosphorothioate modified backbone.

21. A method for preventing an allergic reaction in a subject receiving a blood transfusion, comprising administering to a subject receiving a blood transfusion an immunostimulatory nucleic acid in an effective amount to prevent an allergic reaction to the blood transfusion.

22. The method of claim 21, wherein the blood transfusion is a red blood cell transfusion.

23. The method of claim 21, wherein the blood transfusion is a platelet transfusion.

24. The method of claim 21, wherein the immunostimulatory nucleic acid is a CpG nucleic acid.

25. The method of claim 21, wherein the immunostimulatory nucleic acid has a modified backbone.

26. The method of claim 25, wherein the modified backbone is a phosphorothioate modified backbone.

27. The method of claim 26, wherein the immunostimulatory nucleic acid

with the phosphorothioate modified backbone is free of a CpG motif, and a T-rich motif.

28. The method of claim 21, wherein the immunostimulatory nucleic acid is not a poly-G nucleic acid.

29. The method of claim 21, wherein the subject has cancer.

30. The method of claim 21, wherein the subject is anemic or thrombocytopenic.

31. A method for treating a subject having or at risk of developing cancer, comprising administering to a subject in need of such treatment an immunostimulatory nucleic acid selected from the group consisting of a CpG nucleic acid and a non-CpG nucleic acid, and a cancer medicament that is a hormone therapy.

32. The method of claim 31, further comprising administering a cancer antigen to the subject.

33. The method of claim 31, wherein the hormone therapy is selected from the group consisting of estrogen therapy, anti-estrogen therapy, progestin therapy, androgen blockade, adrenocorticosteroid therapy, synthetic glucocorticoid therapy, androgen therapy, synthetic testosterone analog therapy, aromatase inhibitor therapy, gonadotropin-releasing hormone agonists therapy, somatostatin analog therapy.

34. The method of claim 31, wherein the immunostimulatory nucleic acid has a modified backbone.

35. The method of claim 34, wherein the modified backbone is a phosphorothioate modified backbone.

36. A device for delivering an immunostimulatory nucleic acid to a subject receiving an intravenous injection, comprising an intravenous device selected from the group consisting of an intravenous bag and an intravenous tube, and an immunostimulatory nucleic acid, wherein the immunostimulatory nucleic acid is coated on an internal surface of the intravenous device or is embedded within the intravenous device.

L22 ANSWER 9 OF 15 USPATFULL on STN
2002:72875 Methods and compositions for treating conditions of the eye.
Miller, Joan W., Winchester, MA, UNITED STATES
Gragoudas, Evangelos S., Lexington, MA, UNITED STATES
Renno, Reem Z., Boston, MA, UNITED STATES
US 2002040015 A1 20020404
APPLICATION: US 2001-780142 A1 20010209 (9)
PRIORITY: US 2000-181641P 20000210 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of treating unwanted choroidal neovasculature in a mammal, the choroidal neovasculature comprising endothelial cells, the method comprising the steps of: (a) administering to the mammal an anti-angiogenesis factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature; (b) administering to the mammal an amount of photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature; and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal

neovasculature, wherein damage to the endothelial cells resulting from steps (a), (b), and (c) is greater than that resulting only from steps (b) and (c).

2. The method of claim 1, wherein the mammal is a primate.

3. The method of claim 2, wherein the primate is a human.

4. The method of claim 1, wherein the anti-angiogenesis factor is administered to the mammal prior to administration of the photosensitizer.

5. The method of claim 1, wherein the photosensitizer is an amino acid derivatives, an azo dye, a xanthene derivative, a chlorin, a tetrapyrrole derivative, or a phthalocyanine.

6. The method of claim 5, wherein the photosensitizer is lutetium texaphyrin, a benzoporphyrin, a benzoporphyrin derivative, a hematoporphyrin, or a hematoporphyrin derivative.

7. The method of claim 1, wherein the anti-angiogenesis factor is angiostatin, endostatin, a peptide containing a RGD tripeptide sequence and capable of binding the αvB3 integrin, a COX-2 inhibitor or pigment epithelium derived growth factor.

8. The method of claim 1, wherein occlusion of the choroidal neovasculature resulting from steps (a), (b) and (c) is greater than that resulting from steps (b) and (c) alone.

9. The method of claim 1, wherein the method more selectively occludes choroidal neovasculature relative to the same treatment lacking administration of the anti-angiogenesis factor.

10. A method of treating unwanted choroidal neovasculature in a mammal, the choroidal neovasculature comprising endothelial cells, the method comprising the steps of: (a) administering to the mammal an amount of photosensitizer to permit an effective amount to localize in the neovasculature, the photosensitizer comprising a targeting moiety that binds preferentially to endothelial cells of the neovasculature; and (b) irradiating the neovasculature with a laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature.

11. The method of claim 10, wherein the mammal is a primate.

12. The method of claim 11, wherein the mammal is a human.

13. The method of claim 10, wherein the targeting moiety is a peptide.

14. The method of claim 13, wherein the peptide binds specifically to an α-v β integrin or is an antibody that binds specifically to a vascular endothelial growth factor receptor.

15. The method of claim 14, wherein the integrin is α-v β3 integrin or α-v β5 integrin.

16. The method of claim 14, wherein the antibody is a monoclonal antibody or an antigen binding fragment thereof, a polyclonal antibody or an antigen binding fragment thereof, or a **biosynthetic antibody binding site**.

17. The method of claim 10, wherein the photosensitizer is an amino acid

derivatives, an azo dye, a xanthene derivative, a chlorin, a tetrapyrrole derivative, and a phthalocyanine.

18. The method of claim 17, wherein the photosensitizer is lutetium texaphryin, a benzoporphyrin, a benzoporphyrin derivative, a hematoporphyrin or a hematoporphyrin derivative.

19. The method of claim 10, wherein the targeting moiety enhances the specificity of the photosensitizer to choroidal neovasculature relative to photosensitizer lacking the targeting moiety.

20. A method of treating unwanted choroidal neovasculature in a mammal, the method comprising the steps of: (a) administering to the mammal, an apoptosis-modulating factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature or tissue surrounding the choroidal neovasculature; (b) administering to the mammal an amount of photosensitizer sufficient to permit an effective amount of localize in the choroidal neovasculature; and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, wherein the level of cell damage to the choroidal neovasculature relative to the tissue surrounding the choroidal neovasculature resulting from steps (a), (b) and (c) is greater than that resulting from steps (b) and (c) alone.

21. The method of claim 20, wherein the mammal is a primate.

22. The method of claim 21, wherein the mammal is a human.

23. The method of claim 20, wherein the factor is administered to the primate before administration of the photosensitizer.

24. The method of claim 20, wherein the photosensitizer is an amino acid derivatives, an azo dye, a xanthene derivative, a chlorin, a tetrapyrrole derivative, or a phthalocyanine.

25. The method of claim 20, wherein the photosensitizer is lutetium texaphyrin, a benzoporphyrin, a benzoporphyrin derivative, a hematoporphyrin or a hematoporphyrin derivative.

26. The method of claim 20, wherein the apoptosis modulating factor induces or represses apoptosis.

27. The method of claim 26, wherein the factor is a peptide.

28. The method of claim 27, wherein the peptide selectively binds to neovasculature.

29. The method of claim 27, wherein the peptide induces apoptosis in endothelial cells.

30. The method of claim 29, wherein the peptide comprises an amino acid sequence comprising, in an N- to C-terminal direction, KLAKLAKKLAKLAK (SEQ. ID. NO 1).

31. The method of claim 30, wherein the peptide further comprises an RGD-4C peptide sequence.

32. The method of claim 1, wherein the method ameliorates the symptoms of a disorder selected from the group consisting of age-related macular degeneration, ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, idiopathic disorders, choroiditis, choroidal rupture, overlying

choroid nevi, and inflammatory diseases.

L22 ANSWER 10 OF 15 USPATFULL on STN
2001:186379 Apparatus and method of adaptively coding/decoding interlaced shaped material.
Chun, Sung-Moon, Kyoungki-do, Korea, Republic of
Shin, Dong-Kyoo, Seoul, Korea, Republic of
Moon, Joo-Hee, Seoul, Korea, Republic of
Hyundai Electronics Ind. Co., Ltd., Kyoungki-do, Korea, Republic of (non-U.S. corporation)
US 6307976 B1 20011023
APPLICATION: US 1998-162604 19980929 (9)
PRIORITY: KR 1997-49790 19970929
KR 1998-491 19980110
DOCUMENT TYPE: Utility; GRANTED.
CLM What is claimed is:

1. An apparatus for adaptively coding shape information by using characteristics of the shape information in case of interlaced video, including a coding apparatus for the interlaced video comprising: binary alpha block (BAB) division means for dividing the binary shape information into **BABs** of a predetermined size; coding type mode determining means for determining whether to code said BAB received from said BAB division means from a frame or from a field; switching means for switching said BAB received from said BAB division means according to a coding type mode signal produced by said coding type mode determining means; motion estimation means for estimating a motion from said BAB received from said BAB division means and a previous shape information frame; motion compensation means for compensating said current BAB for the motion using motion information received from said motion estimation means and the previous shape BAB; frame type coding means for receiving said BAB via said switching means and a motion compensated BAB from said motion compensation means and coding the BAB using the motion compensated BAB in unit of frame type; field type coding means for receiving said BAB via said switching means and the motion compensated BAB from said motion compensation means and coding the BAB using the motion compensated BAB in unit of field type; shape reconstructing means for reconstructing the shape information from the BAB received from said frame type coding means and the field type coding means; previous shape memory means for storing the reconstructed shape information received from said shape reconstructing means; overhead coding means for creating overhead information from the motion information received from said motion estimation means and the data received from said frame type coding means and said field type coding means; and multiplexing means for multiplexing the coded data received from said frame type coding means and said field type coding means and said overhead information received from said overhead coding means before transmission.

2. An apparatus according to claim 1, further comprising conversion ratio determining means for determining a conversion ratio of said binary alpha block (BAB), converting the BAB received from said BAB division means and the motion compensated BAB received from said motion compensation means in accordance with the determined conversion ratio, and sending converted **BABs** to said frame type coding means and said field type coding means.

3. An apparatus according to claim 1, further comprising: conversion ratio determining means for determining a conversion ratio of said binary alpha block (BAB), converting the BAB received from said BAB division means and the motion compensated BAB received from said motion compensation means in accordance with the determined conversion ratio,

and sending converted **BABs** to said frame type coding means and said field type coding means; and permuted BAB conversion ratio determining means for determining a conversion ratio of said binary alpha block (BAB), converting the BAB received from said BAB division means and the motion compensated BAB received from said motion compensation means in accordance with the determined conversion ratio, and sending converted **BABs** to said field type coding means.

4. An apparatus according to claim 1, wherein said coding type mode determining means comprises: binary alpha block (BAB) memory means for storing the BAB received from said BAB division means; address generating means for making said BAB memory means output the BAB in units of a frame type or a field type; first shape comparing means for comparing each pair of pixels at the same horizontal location in each line pair comprising an odd and an adjacent even lines in the frame BAB received from said BAB memory means; second shape comparing means for comparing each pair of pixels at the same horizontal location in each line pair comprising an even and an adjacent odd lines in the frame BAB from said BAB memory means; third shape comparing means for comparing pixels at the same horizontal location in each pair of consecutive odd lines in the field BAB received from said BAB memory means; fourth shape comparing means for comparing pixels at the same horizontal location in each pair of consecutive even lines in the field BAB received from said BAB memory means; first to fourth counting means for respectively counting outputs of said first to fourth shape comparing means; first summing means for summing up outputs of said first and second counting means; second summing means for summing up outputs of said third and fourth counting means; and frame/field mode selecting means for comparing outputs of said first and second summing means to select either a field mode coding type or a frame mode coding type and producing a signal of the selected coding type.

5. An apparatus according to claim 1, wherein said coding type mode determining means comprises: binary alpha block (BAB) memory means for storing the BAB received from said BAB division means; address generating means for making said BAB memory means output the BAB in units of a frame type or a field type; first exclusive OR operation means for performing an exclusive OR operation with respect to pairs of pixels at the same horizontal location in consecutive line pairs within a frame BAB received from said BAB memory means; second exclusive OR operation means for receiving an odd field BAB and an even field BAB from said BAB memory means and performing an exclusive OR operation with respect to pairs of pixels at the same horizontal location in consecutive line pairs within each field BAB; first and second summing means for respectively summing up outputs of said first and second exclusive OR operation means; and frame/field mode selecting means for comparing outputs of said first and second summing means to select one of a field and a frame mode coding types.

6. An apparatus according to claim 1, wherein said frame type coding means comprises bordering means and frame scan type and coding means and said field type coding means comprises bordering means and field scan type and coding means.

7. An apparatus for decoding shape information of an object in video, including a decoding apparatus for interlaced scanning comprising: demultiplexing means for demultiplexing input coded data; overhead decoding means for decoding overhead information contained in demultiplexed data received from said demultiplexing means; coding mode decoding means for decoding coding mode data received from said demultiplexing means; switching means for switching coded shape information received from said demultiplexing means according to the

coding mode received from said coding mode decoding means; frame decoding means for decoding the shape information received via said switching means and motion compensated, previous shape information based upon a frame by using said overhead information; field decoding means for decoding the shape information received via said switching means and motion compensated, previous shape information based upon a field by using said overhead information; previous shape memory means for storing previous shape information received from said frame decoding means and said field decoding means; motion compensation means for receiving motion information from said overhead decoding means and the previous shape information from said previous shape memory means, performing motion compensation, and transmitting a result of the motion compensation to said frame decoding means and said field decoding means; and shape reconstructing means for receiving the overhead information from said overhead decoding means and reconstructing the shape information received from said frame decoding means and said field decoding means by using said overhead information.

8. An apparatus according to claim 7, wherein said frame decoding means comprises: bordering means for performing bordering with respect to a binary alpha block (BAB) received from said demultiplexing means; and scan type and decoding means for converting a scan type according to scan type information received from said overhead decoding means and scanning and decoding the frame BAB, and said field decoding means comprises: bordering means for performing bordering with respect to a BAB received from said demultiplexing means; scan type and decoding means for converting a scan type according to scan type information received from said overhead decoding means and scanning and decoding the BAB; and BAB converting means for converting an odd field BAB and an even field BAB received from said scan type and decoding means into a frame BAB.

9. An apparatus according to claim 7, wherein said decoding means is context based arithmetic decoding means.

10. An apparatus for coding interlaced shape information comprising: binary alpha block (BAB) division means for dividing the binary shape information into **BABs** of a predetermined size; coding mode determining means for determining whether to code said BAB received from said BAB division means based upon a frame or a field; switching means for switching said BAB received from said BAB division means according to a coding mode signal produced by said coding mode determining means; motion estimation means for estimating motion from said BAB received from said BAB division means and a previous BAB according to a coding mode received from said coding mode determining means; motion compensation means for compensating the current BAB for the motion by using motion information received from said motion estimation means and the previous BAB; frame type coding means for receiving said BAB via said switching means and a motion compensated BAB from said motion compensation means and coding the BAB using the motion compensated BAB in unit of frame type; field type coding means for receiving said BAB via said switching means and the motion compensated BAB from said motion compensation means and coding the BAB using the motion compensated BAB in unit of field type; shape reconstructing means for reconstructing the shape information from the BAB received from said frame type coding means and the field type coding means; previous shape memory means for storing the reconstructed shape information received from said shape reconstructing means; overhead coding means for creating overhead information from the motion information received from said motion estimation means and the data received from said frame coding means and said field coding means; and multiplexing means for multiplexing the coded data received from said frame coding means and said field coding

means and said overhead information received from said overhead coding means before transmission.

11. A method for adaptively coding shape information by using characteristics of the shape information in case of interlaced video, including an adaptive interlaced shape information coding method comprising the steps of: performing motion compensation with respect to a binary alpha block by using previous frame information; determining a type of said binary alpha block based upon the result of motion estimation; when said binary alpha block is determined to be a type which does not need to be coded, coding and transmitting date indicating the type; when said binary alpha block is type which needs to be coded, determining whether to subject said binary alpha block to frame type coding or to field type coding according to said estimated amount of motion; subjecting said binary alpha block to frame-based coding and transmitting the coded binary alpha block when the frame type coding is determined; and subjecting said binary alpha block to field-based coding and transmitting the coded binary alpha block when the field type coding is determined; and wherein a following formula is used to determine whether to subject said binary alpha block to the frame type coding or to the field type coding according to said estimated amount of motion, so said binary alpha block is determined to be subjected to the field type coding if a left value is larger than a right value in the formula and, alternatively, said binary alpha block is determined to be the subjected to the frame type coding if the left value is less than the right value in the formula: ##EQU4## if(P(2i,j)≠P(2+1,j)), A=1, otherwise, A=0 if(P(2i+1,j)≠P(2i+2,j)), B=1, otherwise, B=0 if(P(2i,j)≠P(2i+2,j)), C=1, otherwise, C=0 if(P(2i+1,j)≠P(i2+3,j), D=1, otherwise, D=0 where P(i,j) is binary shape information data.

L22 ANSWER 11 OF 15 USPATFULL on STN

2001:83742 Method and apparatus for encoding a motion vector of a binary shape signal.

Kim, Jin-Hun, Seoul, Korea, Republic of

Daewoo Electronics Co., Ltd., Seoul, Korea, Republic of (non-U.S. corporation)

US 6243418 B1 20010605

APPLICATION: US 1998-132663 19980812 (9)

PRIORITY: KR 1998-11093 19980330

DOCUMENT TYPE: Utility; Granted.

CLM What is claimed is:

1. A method, for use in a video signal encoder which encodes a video signal comprised of texture information and shape information by selectively using a progressive or an interlaced coding technique, for encoding a motion vector of the shape information, wherein the shape information is divided into a multiplicity of binary alpha blocks (**BABs**) of MxN binary pixels and the texture information has a plurality of macroblocks of the same number of pixels as that of a BAB, M and N being positive integers, respectively, comprising the steps of: (a) deciding an encoding_type representing a more effective coding technique between the progressive and the interlaced coding techniques for encoding a target BAB; (b) detecting, in response to the encoding_type, a motion vector predictor corresponding to the target BAB among candidate motion vector predictors including frame-based and field-based motion vectors for the shape and the texture information; (c) determining the motion vector of the target BAB based on the detected motion vector predictor; and (d) encoding the motion vector of the target BAB.

2. The method according to claim 1, wherein the candidate motion vector

predictors include frame-based and field-based motion vectors for **BABs** which surround the target BAB and have been previously encoded and frame-based and field-based motion vectors for macroblocks which surround the macroblock corresponding to the target BAB and also have been previously encoded, wherein each field-based motion vector has a top- and a bottom-field motion vectors corresponding to a top- and a bottom-field blocks, respectively, of a BAB or a macroblock.

3. The method according to claim 2, wherein, if the progressive coding type is decided as the encoding_type of the target BAB at the step (a), the step (b) detects the motion vector predictor as traversing the candidate motion vector predictors in the order of the frame-based motion vectors for the shape information, the field-based motion vectors for the shape information, the frame-based motion vectors for the texture information and the field-based motion vectors for the texture information.

4. The method according to claim 3, wherein, at the step (b), if one of the field-based motion vectors is selected to detect the motion vector predictor, the step (b) includes the steps of: (b11) calculating a mean of the top- and the bottom-field motion vectors of the selected field-based motion vector; and (b12) determining the mean as the motion vector predictor.

5. The method according to claim 2, if the interlaced coding type is decided as the encoding_type of the target BAB at the step (a), the step (b) includes the steps of: (b21) dividing the target BAB into a top- and a bottom-field **BABs**; and (b22) determining the motion vector predictor having a top- and a bottom-field motion vector predictors corresponding to the top- and the bottom-field **BABs**, respectively, as traversing the candidate motion vectors in the order of the field-based motion vectors for the shape information, the frame-based motion vectors for the shape information, the field-based motion vectors for the texture information and the frame-based motion vectors for the texture information.

6. The method according to claim 5, wherein, at the step (b22), if one of the frame-based motion vectors is selected to detect the top- and the bottom-field motion vector predictors, the step (b22) assigns the selected frame-based motion vector to the top- and the bottom-field **BABs** as the top- and the bottom-field motion vector predictors, respectively.

7. The method according to claim 5, wherein, at the step (b22), if one of the field-based motion vectors is selected to detect the top- and the bottom-field motion vector predictors, the step (b22) determines the top-field motion vector of the selected field-based motion vector as the top-field motion vector predictor and decides the bottom-field motion vector thereof as the bottom-field motion vector predictor.

8. The method according to claim 5, wherein, at the step (b22), if one of the field-based motion vectors is chosen to detect the top- and the bottom-field motion vector predictors, the step (b22) assigns the bottom-field motion vector of the selected field-based motion vector to the top- and the bottom-field **BABs** of the target BAB as the top- and the bottom-field motion vector predictors, respectively.

9. An apparatus, for use in a video signal encoder which encodes a video signal comprised of texture information and shape information by selectively using a progressive or an interlaced coding technique, for encoding a motion vector of the shape information, wherein the shape information is divided into a multiplicity of binary alpha blocks (**BABs**) of MxN binary pixels and the texture information has a

plurality of macroblocks of the same number of pixels as that of a BAB, M and N being positive integers, respectively, which comprises: means for determining a more effective coding technique between the progressive and the interlaced coding techniques for encoding a target BAB to thereby produce an encoding_type signal; means for providing, in response to the encoding_type signal, either the target BAB or a top- and a bottom-field **BABs** which are generated by dividing the target BAB according to the interlaced coding technique; a motion vector predictor (MVP) determination means for detecting a frame-based or a field-based motion vector predictor corresponding to either the target BAB or the top- and the bottom-field **BABs** among candidate motion vector predictors including frame-based and field-based motion vectors for the shape and the texture information; means for deciding the motion vector corresponding to the target BAB by using the detected motion vector predictor; and means for encoding the motion vector corresponding to the target BAB.

10. The apparatus as recited in claim 9, wherein the candidate motion vector predictors include frame-based and field-based motion vectors corresponding to **BABs** which surround the target BAB and have been previously encoded and frame-based and field-based motion vectors corresponding to macroblocks which surround the macroblock corresponding to the target BAB and also have been previously encoded, wherein each field-based motion vector has a top- and a bottom-field motion vectors corresponding to a top- and a bottom-field blocks, respectively, of a BAB or a macroblock.

11. The apparatus as recited in claim 10, wherein the MVP determination means selects the frame-based motion vector predictor by traversing the candidate motion vector predictors in the order of the frame-based motion vectors for the shape information, the field-based motion vectors for the shape information, the frame-based motion vectors for the texture information and the field-based motion vectors for the texture information.

12. The apparatus as recited in claim 11, wherein, if the frame-based motion vector predictor is detected among the field-based motion vectors for the shape and the texture information, the MVP determination means calculates a mean of the top- and the bottom-field motion vectors of the detected field-based motion vector and determines the mean as the frame-based motion vector predictor.

13. The apparatus as recited in claim 10, wherein the MVP determination means chooses the field-based motion vector predictor, including a top- and a bottom-field motion vector predictors corresponding to the top- and the bottom-field **BABs**, respectively, by traversing the candidate motion vectors in the order of the field-based motion vectors for the shape information, the frame-based motion vectors for the shape information, the field-based motion vectors for the texture information and the frame-based motion vectors for the texture information.

14. The apparatus as recited in claim 13, wherein, if the field-based motion vector predictor is detected among the frame-based motion vectors for the shape and the texture information, the MVP determination means assigns the detected frame-based motion vector to the top- and the bottom-field **BABs** as the top- and the bottom-field motion vector predictors, respectively.

15. The apparatus as recited in claim 13, wherein, if the field-based motion vector predictor is detected among the field-based motion vectors for the shape and the texture information, the MVP determination means decides the top-field motion vector of the detected field-based motion

vector as the top-field motion vector predictor and the bottom-field motion vector thereof as the bottom-field motion vector predictor.

16. The apparatus as recited in claim 13, wherein, if the field-based motion vector predictor is detected among the field-based motion vectors for the shape and the texture information, the MVP determination means assigns the bottom-field motion vector of the detected field-based motion vector to the top- and the bottom-field **BABs** of the target BAB as the top- and the bottom-field motion vector predictors, respectively.

L22 ANSWER 12 OF 15 USPATFULL on STN
2000:21399 Methods for the detection of cervical cancer.
Keesee, Susan K., Harvard, MA, United States
Obar, Robert, Walpole, MA, United States
Wu, Ying-Jye, Framingham, MA, United States
Matritech, Inc., Newton, MA, United States (U.S. corporation)
US 6027905 20000222
APPLICATION: US 1997-989045 19971211 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of screening for cervical cancer in a human, the method comprising: (a) obtaining a sample isolated from said human; and (b) detecting in said sample the presence of a protein characterized as being detectable at a higher level in a cervical cancer cell than in a normal cervical cell and comprising an amino acid sequence selected from the group of sequences consisting of SEQ ID NO: 1; SEQ ID NO:2; SEQ ID NO:3; SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; SEQ ID NO:9; and SEQ ID NO: 10, which if present is indicative of cervical cancer in said human.

2. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO: 1.

3. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:2.

4. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:3.

5. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:4.

6. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:5.

7. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:6.

8. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:7.

9. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:8.

10. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:9.

11. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:10.

12. The method of claim 1, wherein said sample is a tissue or body fluid sample.

13. The method of claim 1, wherein said sample is a biopsy sample.

14. The method of claim 1, wherein said sample is a cervical cell sample.

15. The method of claim 1, wherein said sample is a Papanicolaou smear.

16. A method of screening for cervical cancer in a human, the method comprising the steps of: (a) contacting a sample derived from said human with a binding moiety that binds specifically to a cervical cancer-associated protein to produce a binding moiety-cervical cancer-associated protein complex, wherein said binding moiety is selected from the group consisting of an antibody, an antibody fragment and a **biosynthetic antibody binding site**, and wherein said binding moiety binds specifically to a protein comprising the amino acid sequence set forth in SEQ ID NO: 10; and (b) detecting the presence of said complex, which if present is indicative of the presence of cervical cancer in said human.

17. The method of claim 16, wherein said cervical cancer-associated protein is further characterized as being present at a higher amount in a human cervical cancer cell than in a normal human cervical cell, as determined by two dimensional gel electrophoresis.

18. The method of claim 16, wherein said sample is a tissue or body fluid sample.

19. The method of claim 16, wherein said sample is a biopsy sample.

20. The method of claim 16, wherein said sample is a Papanicolaou smear.

21. The method of claim 16, wherein said sample is a cervical cell sample.

22. The method of claim 16, wherein said binding moiety is an antibody.

23. The method of claim 22, wherein said antibody is a monoclonal antibody.

24. The method of claim 22, wherein said antibody is labeled with a detectable moiety.

25. The method of claim 23, wherein said monoclonal antibody is labeled with a detectable moiety.

26. The method of claim 1, wherein absence of a detectable amount of said protein is indicative of the absence of cervical cancer.

27. The method of claim 1, further comprising the additional steps of (c) measuring an amount of said protein in said sample and (d) comparing the amount of said protein in said sample with the amount of said protein in a prior sample previously obtained from said human, wherein an increae in amount of said protein in said sample relative to the amount of said protein in said prior sample is indicative of progression of said cervical cancer.

28. The method of claim 16, wherein absence of a detectable amount of said complex is indicative of the absence of cervical cancer.

29. The method of claim 16, further comprising the additional steps of (c) measuring an amount of said protein in said sample and (d) comparing the amount of said protein in said sample with the amount of said protein in a prior sample previously obtained from said human, wherein an increase in amount of said protein in said sample relative to the amount of said protein in said prior sample is indicative of progression of said cervical cancer.

L22 ANSWER 13 OF 15 USPATFULL on STN
1999:4349 Methods and compositions for the detection of cervical cancer.
Keesee, Susan K., Harvard, MA, United States
Obar, Robert, Walpole, MA, United States
Wu, Ying-Jye, Framingham, MA, United States
Matritech, Inc., Newton, MA, United States (U.S. corporation)
US 5858683 19990112
APPLICATION: US 1996-705660 19960830 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of detecting cervical cancer in a human, the method comprising: detecting in a sample isolated from said human the presence of a protein comprising an amino acid sequence selected from the group of sequences consisting of SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:22; SEQ ID NO:23; SEQ ID NO:24; SEQ ID NO:25; and SEQ ID NO:26, the presence of said protein being indicative of cervical cancer in said human.

2. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:19.

3. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:20.

4. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:21.

5. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:22.

6. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:23.

7. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:24.

8. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:25.

9. The method of claim 1, wherein said protein comprises the amino acid sequence set forth in SEQ ID NO:26.

10. The method of claim 1, wherein said sample is a tissue or body fluid sample.

11. The method of claim 1, wherein said sample is a biopsy sample.

12. The method of claim 1, wherein said sample is a cervical cell sample.

13. The method of claim 1, wherein said sample is a Papanicolaou smear.

14. A method of detecting cervical cancer in a human, the method comprising the steps of: (a) contacting a sample derived from said human with a binding moiety that binds specifically to a cervical cancer-associated protein to produce a binding moiety-cervical cancer-associated protein complex, wherein said binding moiety is selected from the group consisting of an antibody, an antibody fragment and a **biosynthetic antibody binding site**, and wherein said binding moiety binds specifically to a protein comprising the amino acid sequence set forth in SEQ ID NO:26; and (b) detecting the presence of said complex, the presence of said complex being indicative of the presence of cervical cancer in said human.

15. The method of claim 14, wherein said cervical cancer-associated protein is further characterized as being detectable at a higher level in a human cervical cancer cell than in a normal human cervical cell, as determined by two dimensional gel electrophoresis.

16. The method of claim 14, wherein said sample is a tissue or body fluid sample.

17. The method of claim 14, wherein said sample is a biopsy sample.

18. The method of claim 14, wherein said sample is a Papanicolaou smear.

19. The method of claim 14, wherein said sample is a cervical cell sample.

20. The method of claim 14, wherein said binding moiety is an antibody.

21. The method of claim 20, wherein said antibody is a monoclonal antibody.

22. The method of claim 20, wherein said antibody is labeled with a detectable moiety.

23. The method of claim 21, wherein said monoclonal antibody is labeled with a detectable moiety.

L22 ANSWER 14 OF 15 USPATFULL on STN
1998:82873 Binding proteins to malignant cell type markers of the interior nuclear matrix.
Toukatly, Gary, Amhurst, NH, United States
Lidgard, Graham P., Wellesley, MA, United States
Matritech, Inc., Newton, MA, United States (U.S. corporation)
US 5780596 19980714
APPLICATION: US 1995-467781 19950606 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A composition comprising an isolated binding protein selected from the group consisting of an antibody, an antigen binding fragment thereof, and a **biosynthetic antibody binding site** that binds specifically to a protein comprising the amino acid sequence defined by SEQ ID NO: 2.

2. The composition of claim 1 wherein said binding protein is an antibody.

3. The composition of claim 1 wherein said binding protein is an antibody fragment comprising an antigen binding site.

4. A method of manufacturing an antibody for use in the detection of malignant cell types, the method comprising the steps of: (a) combining a substantially pure protein or protein fragment encoded by the DNA of SEQ ID NO: 1 with an adjuvant to form a composition suitable for injection into a mammal; (b) injecting the composition into said mammal thereby to produce in said mammal an antibody which binds specifically to said protein or protein fragment; and (c) isolating said antibody from said mammal.

5. A composition comprising the binding protein of claim 1 in admixture with a pharmaceutically acceptable carrier.

6. A composition comprising the binding protein of claim 2 in admixture with a pharmaceutically acceptable carrier.

7. A composition comprising an antibody produced by the process of claim 4 in admixture with a pharmaceutically acceptable carrier.

8. The composition of claim 2, wherein said antibody is a monoclonal antibody.

9. The composition of claim 1 wherein said binding protein further comprises a detectable moiety bound thereto.

10. The composition of claim 2 wherein said antibody further comprises a detectable moiety bound thereto.

L22 ANSWER 15 OF 15 USPATFULL on STN
87:14402 Ball throwing machine.
Kholin, Boris G., Sumy, USSR
Sumsky Filial Kharkkovskogo Politeknicheskogo Instituta, Sumy, USSR (non-U.S. corporation)
US 4646709 19870303
WO 8602010 19860410
APPLICATION: US 1986-878969 19860509 (6)
WO 1985-SU18 19850228 19860509 PCT 371 date 19860509 PCT 102(e) date
PRIORITY: SU 1984-3791133 19840928
DOCUMENT TYPE: Utility; Granted.
CLM What is claimed is:
1. A ball throwing machine comprising a ball (5) supply pipe (4) connected to a base (3), an impeller (9) with a hammer (10) mounted on a drive shaft (8) supported by the base (3) for imparting angular motion to the impeller (9) in a plane extending transversely with respect to the drive shaft (8), a follower (11) connected to the base (3) and designed for moving balls (5) fed from the pipe (4) toward the position for projection, the follower (11) operatively connected to the impeller (9) for their timed movement, characterized in that the follower (11) has on the side thereof facing toward the impeller (9) at least two support tabs (15), the free ends (16) of which being directed toward the outlet end (7) of the pipe (4) and adapted to receive and retain a next ball (5), and for that purpose the support tabs (15) are spaced from each other at a distance smaller than the ball (5) diameter and greater than the width of the hammer (10) of the impeller (9) and positioned in such a manner as to let the hammer (10) of the impeller (9) pass therebetween.

2. A machine according to claim 1, characterized in that said support tabs (15) comprise leaf springs, the free ends (16) of the tabs bearing against said pipe (4) adjacent to the outlet end (7) thereof at the moment when the next one of said balls (5) is supplied from said pipe (4) to said two support tabs (15).

3. A machine according to claim 1, characterized in that said follower (11) comprises an arm having a pivot pin (17) mounted on said base (3) in parallel with said shaft (8).

4. A machine according to claim 3, characterized in that a snut-off plate (19) is provided on the free end (18) of the arm (13) to extend transversely with respect to the arm (13), the plate (19) being directed away from said two support **babs** (15) and being adapted to retain the following one of said balls (5) within said pipe (4) when said next ball (5) is retained on said two support tabs (15) in the position for projection.

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=> d his

     (FILE 'HOME' ENTERED AT 20:15:09 ON 27 SEP 2006)

     FILE 'USPATFULL' ENTERED AT 20:15:17 ON 27 SEP 2006
                E HUSTON JAMES S/IN
L1           26 S E3
L2            7 S L1 AND (FRAMEWORK REGION?/CLM)
                E OPPERMANN H/AU
                E E12
L3          101 S E3-E5
L4           84 S L3 NOT L1
L5            0 S L4 AND (FRAMEWORK REGION?/CLM)

     FILE 'WPIDS' ENTERED AT 20:20:02 ON 27 SEP 2006
                E HUSTON J S/IN
L6           20 S E3
L7            9 S L6 AND (FRAMEWORK REGION?)
                E OPPERMANN H/IN
L8          138 S E3
L9          126 S L8 NOT L6
L10           0 S L9 AND (FRAMEWORK REGION?)

     FILE 'MEDLINE' ENTERED AT 20:23:24 ON 27 SEP 2006
                E HUSTON J S/AU
L11          35 S E3
L12           0 S L11 AND (FRAMEWORK REGION?)
                E OPPERMANN H/AU
L13          75 S E3
L14          65 S L13 NOT L11
L15           1 S L14 AND (FRAMEWORK)

     FILE 'USPATFULL' ENTERED AT 20:32:29 ON 27 SEP 2006
L16         380 S (FRAMEWORK REGION?/CLM)
L17         197 S L16 AND (COMPLEMENTARITY DETERMINING REGION?/CLM)
L18          17 S L17 AND LINKER/CLM
L19          11 S L18 NOT L1
L20          16 S (BIOSYNTHETIC ANTIBODY BINDING SITE?/CLM OR BABS/CLM)
L21          15 S L20 NOT L1
L22          15 S L21 NOT L19

=> s (single-chain Fv/clm or scFv/clm or sFv/clm)
        371319 SINGLE/CLM
        119932 CHAIN/CLM
          1449 FV/CLM
           299 SINGLE-CHAIN FV/CLM
                 ((SINGLE(W)CHAIN(W)FV)/CLM)
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           741 SCFV/CLM
           156 SFV/CLM
L23       1098 (SINGLE-CHAIN FV/CLM OR SCFV/CLM OR SFV/CLM)

=> s l23 and (predetermined antigen/clm)
        784554 PREDETERMINED/CLM
         17539 ANTIGEN/CLM
            59 PREDETERMINED ANTIGEN/CLM
                 ((PREDETERMINED(W)ANTIGEN)/CLM)
L24          2 L23 AND (PREDETERMINED ANTIGEN/CLM)

=> s l24 not l1
L25          2 L24 NOT L1

=> d l25,cbib,clm,1-2

L25  ANSWER 1 OF 2  USPATFULL on STN
2005:43692 Immunoglobulin having particular framework scaffold and methods of
    making and using.
    Zhang, Mei-Yun, Frederick, MD, UNITED STATES
    Schillberg, Stefan, Aachen, GERMANY, FEDERAL REPUBLIC OF
    Zimmermann, Sabine, Koeln, GERMANY, FEDERAL REPUBLIC OF
    Fiore, Stefano di, Neubrandenburg, GERMANY, FEDERAL REPUBLIC OF
    Emans, Neil, Thiminster-clermont, BELGIUM
    Fischer, Rainer, Monschau, GERMANY, FEDERAL REPUBLIC OF
    US 2005037420 A1 20050217
    APPLICATION: US 2004-489328  A1  20040827 (10)
    WO 2002-US29003 20020913
    PRIORITY: US 2001-318904P  20010914 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. An immunoglobulin molecule comprising one or more heavy chain
       framework regions, HFR1, HFR2, HFR3, and HFR4, and one or more light
       chain framework regions, LFR1, LFR2, LFR3 and LFR4, and further
       comprising complementarity determining regions, CDR-H1, CDR-H2, CDR-H3,
       and/or CDR-L1, CDR-L2 and CDR-L3, said immunoglobulin molecule having
       the structure:  (a) HFR1--CDR-H1--HFR2--CDR-H2--HFR3--CDR-H3--HFR4 or
       (b) LFR1--CDR-L1--LFR27-CDR-L2--LFR3--CDR-L3--LFR4,  or (a) and (b)
       wherein,  (i) HFR1 is a first framework region in (b) consisting of a
       sequence of about 30 amino acid residues;  (ii) HFR2 is a second
       framework region in (b) consisting of a sequence of about 14 amino acid
       residues;  (iii) HFR3 is a third framework region in (b) consisting of a
       sequence of about 29 to about 32 amino acid residues;  (iv) HFR4 is a
       framework region of (b) consisting of a sequence of 7 to about 9 amino
       acid residues, wherein the first amino acid residue is tryptophan (Trp);
       (v) CDR-H1 is a first complementary determining region;  (vi) CDR-H2 is
       a second complementary determining region;  (vii) CDR-H3 is a third
       complementary determining region;  (viii) LFR1 is a first framework
       region consisting of a sequence of about 22 to about 23 amino acid
       residues;  (ix) LFR2 is a second framework region consisting of a
       sequence of about 13 to about 16 amino acid residues, wherein a Pro or
       Leu must be at position 10 if the sequence is 15 amino acid residues
       long or position 11 if the sequence is 16 amino acid residues long;  (x)
       LFR3 is a third framework region consisting of a sequence of about 32
       amino acid residues;  (xi) LFR4 is a fourth framework region consisting
       of a sequence of about 12 to about 13 amino acid residues, wherein the
       first amino acid residue is Phe;  (xii) CDR-L1 is a first complementary
       determining region;  (xiii) CDR-L2 is a second complementary determining
       region;  (xiv) CDR-L3 is a third complementary determining region,
       wherein the length of the CDRs and the framework regions and positions
       of the amino acid residues in the CDRs and the framework regions are in
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accordance with the Kabat numbering system.

2. The immunoglobulin molecule of claim 1 wherein the HFR3 consists of 29-32 amino acid residues, wherein the first amino acid residue is Arginine (Arg) and the tenth amino acid residue is glutamine (Gln).

3. The immunoglobulin molecule of claim 1, comprising a CDR-H1 consisting of about 5 to about 7 amino acid residues, a CDR-H2 consisting of about 16 to about 18 amino acid residues, CDR-H3 consisting of about 9 to about 21 amino acid residues, a CDR-L1 consisting of about 5 to about 14, CDR-L2 consisting of about 5 to about 7 amino acid residues, CDR-L3 consisting of about 5 to about 15 amino acid residues, LFR1 consists of about 22 amino acid residues, LFR2 consists of about 16 amino acid residues, LFR3 consists of 32 amino acid residues and LFR4 consists of about preferably about 13 amino acid residues.

4. The immunoglobulin molecule of claim 3 wherein the CDR-H1 consists of about 5 amino acid residues, the CDR-H2 consists of about 17 amino acid residues, the CDR-H3 consists of 9 to about 19 amino acid residues, the CDR-L1 consists of 8, 9, 10 or 13 amino acid residues, the CDR-L2 consists of 7 amino acid residues and the CDR-L3 consists of about 8 to about 12 amino acid residues.

5. The immunoglobulin molecule of claim 4, wherein the CDR-H3 consist of about 14 amino acid residues to about 19 amino acid residues.

6. An immunoglobulin molecule of claim 1 wherein said at least one of said heavy chain framework regions is selected from the group consisting of an HFR1 comprising SEQ ID NO: 1, an HFR2 comprising SEQ ID NO: 2, an HFR3 comprising SEQ ID NO: 3, and an HFR4 comprising SEQ ID NO: 4, and wherein at least one of said light chain framework regions is selected from the group consisting of an LFR1 comprising SEQ ID NO: 5, an LFR2 comprising SEQ ID NO: 6, an LFR3 comprising SEQ ID NO: 7 and an LFR4 comprising SEQ ID NO: 8.

7. The immunoglobulin molecule of claim 1, wherein: HFR1 comprises SEQ ID NO: 1; HFR2 comprises SEQ ID NO: 2; HFR3 comprises SEQ ID NO: 3; HFR4 comprises SEQ ID NO: 4; LFR1 comprises SEQ ID NO: 5; LFR2 comprises SEQ ID NO: 6; LFR3 comprises SEQ ID NO: 7, and; LFR4 comprises SEQ ID NO: 8.

8. The immunoglobulin of claim 7 wherein amino acid residue at positions 18, 19 or 20 in SEQ ID NO: 3 are absent and are not substituted by any other amino acid.

9. The immunoglobulin of claim 7 wherein the amino acid residue at position 6 in SEQ ID NO:6 is absent and is not substituted by any other amino acid.

10. The immunoglobulin of claim 7 wherein amino acid residue at position 10 in SEQ ID NO: 8 is absent and not substituted by any other amino acid.

11. The immunoglobulin of claim 1 wherein the immunoglobulin molecule comprises: (a) HFR1 consisting of SEQ ID NO:1, HFR2 consisting of SEQ ID NO:2, HFR3 consisting of SEQ ID NO:3, and HFR4 consisting of SEQ ID NO:4, or (b) LFR1 consisting of SEQ ID NO:5, LFR2 consisting of SEQ ID NO:6, LFR3 consisting of SEQ ID NO:7 and LFR4 consisting of SEQ ID NO: 8, or variants of (a) or (b) having conservative substitutions in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7 or 8.

12. The immunoglobulin of claim 11 wherein: CDR-L1 is 5-14 amino acid residues in length, CDR-L2 is 5-7 amino acid residues in length, CDR-L3 is 5-15 amino acid residues in length CDR-H1 is 5-8 amino acid residues in length, CDR-H2 is 16-18 amino acid residues in length, and CDR-H3 is 9-19 amino acid residues in length.

13. The immunoglobulin molecule of claim 1 further comprising a cellular targeting signal and/or a tag.

14. The immunoglobulin molecule of claim 1 wherein said cellular targeting signal is selected from the group consisting of apoplastic targeting peptide, an endoplasmic reticulum targeting peptide, a vacuole targeting peptide, protein body targeting peptide and a chloroplast targeting peptide.

15. The isolated immunoglobulin molecule of claim 1 having an amino acid sequence comprising: (a) HFR1 consisting of SEQ ID NO:1, HFR2 consisting of SEQ ID NO:2, HFR3 consisting of SEQ ID NO:3, and HFR4 consisting of SEQ ID NO:4, and (b) LFR1 consisting of SEQ ID NO:5, LFR2 consisting of SEQ ID NO:6, LFR3 consisting of SEQ ID NO:7 and LFR4 consisting of SEQ ID NO: 8, wherein (i) CDR-H1 consists of about 5 to about 7 amino acid residues, (ii) CDR-H2 consists of about 16 to about 18 amino acid residues, (iii) CDR-H3 consists of about 9 to about 21 amino acid residues, (iv) CDR-L1 consists of about 5 to about 14, (v) CDR-L2 consists of about 5 to about 7 amino acid residues, (vi) CDR-L3 consists of about 5 to about 15 amino acid residues.

16. The isolated immunoglobulin molecule of claim 15 wherein: CDR-H1 consists of about 5 amino acid residues, CDR-H2 consists of about 17 amino acid residues, CDR-H3 consists of 9 to about 19 amino acid residues, CDR-L1 consists of 8, 9, 10 or 13 amino acid residues, CDR-L2 consists of 7 amino acid residues and CDR-L3 consists of about 8 to about 12 amino acid residues.

17. The immunoglobulin molecule of claim 16 wherein CDR-H3 consists of about 14 to about 19 amino acid residues.

18. The immunoglobulin molecule of claim 1, 11 or 15 further comprising a linker which joins (a) to (b).

19. A composition comprising the immunoglobulin molecule of the claim 1.

20. The composition of claim 19, wherein said composition is a plant composition.

21. A population of isolated immunoglobulin molecules produced by, (a) expressing a plurality of nucleic acid molecules encoding the immunoglobulin molecules of claim 1 in a host cell, to produce a population of immunoglobulin molecules, and (b) isolating the expressed population of immunoglobulin molecules.

22. An isolated nucleic acid molecule encoding the immunoglobulin molecule of claim 1.

23. The isolated nucleic acid molecule of claim 22 comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO; 13 and SEQ ID NO; 14.

24. An isolated nucleic acid molecule encoding an immunoglobulin molecule variable domain framework region wherein said framework region comprises an amino acid sequence selected from the group consisting of

SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO:8.

25. The isolated nucleic acid molecule of claim 21 wherein said immunoglobulin molecule comprises: (a) an immunoglobulin heavy chain variable domain comprising framework regions SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4, or (b) an immunoglobulin light chain variable domain comprising framework regions SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO:8.

26. A recombinant library comprising one or more isolated nucleic acid molecule of claim 22.

27. A vector comprising an isolated nucleic acid molecule of claim 22 in operable linkage with a promoter.

28. The vector of claim 27, wherein the promoter is selected from a group consisting of a tissue specific, an inducible, a constitutive, a developmentally regulated and a temporally regulated promoter.

29. The vector of claim 28 wherein the tissue specific promoter is a seed specific promoter, root specific promoter or leaf specific promoter.

30. The vector of claim 28, wherein the seed specific promoter is a glutelin-1 promoter.

31. The vector of claim 28, wherein the inducible promoter is an auxin inducible promoter, a heat shock inducible promoter, a light inducible promoter or a wounding inducible promoter.

32. The vector of claim 28, wherein the constitutive promoter is a cauliflower mosaic virus 35s promoter or an ubiquitin promoter.

33. The vector of claim 28, wherein the developmentally regulated promoter is an alpha tubulin promoter or a soybean SbPRP1 promoter.

34. The vector of claim 27 comprising a nucleotide sequence encoding a cellular targeting peptide.

35. The vector of claim 34, wherein the cellular targeting peptide is an apoplastic targeting peptide, an endoplasmic reticulum targeting peptide, a vacuole targeting peptide, a chloroplast targeting peptide and a protein body targeting peptide.

36. A host cell comprising a nucleic acid molecule of claim 22.

37. The host cell of claim 36 wherein said host is bacterial cell, a yeast cell, an algae cell, an insect cell, a mammalian cell or a plant cell.

38. The host cell of claim 35, wherein the nucleic acid molecule encoding the immunoglobulin molecule is in operable linkage with a promoter.

39. The host cell of claim 36 wherein said host cell is a is monocotyledonous plant cell.

40. The host cell of claim 36, wherein said host cell is a dicotyledonous plant cell.

41. The host cell of claim 39, wherein the monocotyledonous plant is

selected from the group consisting of amaranth, barley, maize, oat, rice, sorghum and wheat.

42. The host cell of claim 40, wherein the dicotyledonous plant is selected from the group consisting of tobacco, tomato, ornamentals, potato, sugarcane, soybean, cotton, canola, alfalfa and sunflower.

43. The host cell of claim 37 wherein said host cell is selected from the group consisting of E. coli cells, CHO cells, and COS cells.

44. A method for generating a recombinant library of nucleic acid molecules encoding immunoglobulin molecules having identical framework regions wherein said immunoglobulins accumulate to high levels in a host cell, said method comprising the steps of (a) introducing a population of nucleic acid molecules encoding immunoglobulin molecules comprising avian framework regions into host cells to generate transformed host cells, (b) assaying said transformed host cells for expression of said nucleic acid molecules, (c) identifying transformed host cells producing levels of immunoglobulin molecules that are at least 0.15% of total cellular protein, (d) isolating the immunoglobulin-encoding nucleic acid molecules from the transformed host cells identified in (c), (e) determining the amino acid sequence of framework regions of the immunoglobulin molecules encoded by the nucleic acid molecules of (d) (f) identifying which amino acid residue positions in the framework regions of (e) are conserved among the immunoglobulin molecules, (g) preparing a consensus sequence for the framework regions of (d) having the conserved amino acid residues identified in (f) (h) preparing one or more nucleic acid molecules encoding immunoglobulin molecules having the framework regions of (g) and complementarity determining regions (CDRs) to form a recombinant library of nucleic acid molecules encoding immunoglobulin molecules having identical framework regions

45. The method of claim 44, wherein the immunoglobulin molecule comprises CDRs of an avian, piscean or mammalian antibody.

46. The method of claim 45, wherein the mammalian antibody is a camelid, murine or human antibody.

47. The method of claim 44, wherein the immunoglobulin molecules are selected from the group consisting of immunoglobulin heavy chain or light chain variable domains (V_L or V_H), **scFv**, diabodies, triabodies and tetrabodies.

48. The method of claim 44, wherein the nucleic acid molecules in (f) comprise randomized CDR-encoding sequences.

49. A method for identifying nucleic acid molecules of claim 44(f) that encode an immunoglobulin that binds to a preselected antigen comprising expressing said nucleic acid molecules to produce an immunoglobulin, assaying the binding of said immunoglobulin to the preselected antigen and identifying the nucleic acid molecule that encodes the immunoglobulin that binds to said preselected antigen.

50. The method of claim 44, wherein the isolated nucleic acid molecule of step (a) further comprises a nucleotide sequence that encodes a cellular targeting peptide, such that said nucleic acid molecule of step (a) encodes a fusion of the immunoglobulin molecule and the cellular targeting peptide.

51. The method of claim 44, wherein steps (a) through (h) may be repeated.

52. A method for producing a plant resistant to a pathogen comprising transforming a plant cell with a nucleic acid molecule of claim 19 wherein said nucleic acid encodes an immunoglobulin molecule that is a specific for said pathogen (a) regenerating a plant from said transformed cells, and (b) growing said regenerated plant, under conditions which promote expression of said nucleic acid molecule, wherein expression of said nucleic acid molecule confers resistance to said pathogen.

53. The method of claim 52, wherein the pathogen is a virus, a bacteria, a mycoplasm, a fungus, a nematode or an insect.

54. A method for preparing a recombinant library expressing immunoglobulin molecules or domains thereof which comprise (a) a heavy chain variable domain having the structure HFR1--CDR-H1--HFR2--CDR-H2--HFR3--CDR-H3--HFR4 and/or (b) a light chain variable domain having the structure LFR1--CDR-L1--LFR2--CDR-L2--LFR3--CDR-L3--LFR4, wherein (i) HFR1 is a first framework region in (b) consisting of a sequence of about 30 amino acid residues; (ii) HFR2 is a second framework region in (b) consisting of a sequence of about 14 amino acid residues; (iii) HFR3 is a third framework region in (b) consisting of a sequence of about 29 to about 32 amino acid residues, wherein the first amino acid residue is Arginine (Arg) and the tenth amino acid residue is either leucine (Leu) or proline (Pro); (iv) HFR4 is a framework region of (b) consisting of a sequence of 7 to about 9 amino acid residues wherein the first amino acid residue is tryptophan (Trp); (v) CDR-H1 is a first complementary determining region, (vi) CDR-H2 is a second complementary determining region; (vii) CDR-H3 is a third complementary determining region; (viii) LFR1 is a first framework region consisting of a sequence of about 22 to about 23 amino acid residues; (ix) LFR2 is a second framework region consisting of a sequence of about 13 to about 16 amino acid residues; (x) LFR3 is a third framework region consisting of a sequence of about 32 amino acid residues; (xi) LFR4 is a fourth framework region consisting of a sequence of about 12 to about 13 amino acid residues wherein the first amino acid residue is Phe; (xii) CDR-L1 is a first complementary determining region; (xiii) CDR-L2 is a second complementary determining region; (xiv) CDR-L3 is a third complementary determining region, wherein said method comprises preparing one or more nucleic acid molecules encoding the immunoglobulin molecules, or domains thereof, and expressing said nucleic acid molecules in an appropriate host cell wherein expression of said nucleic acid produces a recombinant library expressing the immunoglobulin molecules or the domains thereof.

55. A method for identifying an immunoglobulin molecule of the recombinant library of claim 54 which binds to a **predetermined antigen** comprising contacting the immunoglobulin molecules with the **predetermined antigen** and assaying for binding therebetween.

56. The method of claim 55 further comprising identifying the nucleic acid molecule that encodes the immunoglobulin molecule or domain thereof identified in claim 56.

57. A method for preparing a transgenic plant comprising one or more immunoglobulin molecule, comprising: (a) introducing a nucleic acid molecule of claim 20 into a plant cell to generate a transformed plant cell; (b) regenerating a transgenic plant from said transformed plant cell; and growing said transgenic plant under conditions suitable for production of said immunoglobulin molecule from said nucleic acid molecule.

58. The method of claim 57 wherein the immunoglobulin molecule is an avian derived immunoglobulin molecule.

59. A transgenic plant produced by the method of claim 57, wherein the immunoglobulin molecule is a VL, VH, **scFv**, diabody, triabody or tetrabody.

60. A seed of the transgenic plant of claim 57.

61-67. (Cancelled)

68. A method for producing an immunoglobulin molecule having a chimeric variable domain comprising: (a) determining amino acid sequence of an avian immunoglobulin molecule comprising a variable domain, wherein said variable domain contains framework regions, and complementary determining regions (CDRs) and determining amino acid sequence of a preselected immunoglobulin molecule, which is specific for an antigen, said preselected immunoglobulin comprising a variable domain which contains framework regions and CDRs, wherein the framework regions and CDRs of the immunoglobulin molecules are in accordance with Kabat's numbering system, (b) comparing the amino acid sequences of the variable domains of the avian immunoglobulin and the preselected immunoglobulin to identify differences in amino acid residues at corresponding positions in the avian and preselected antibody framework regions and CDRs that are necessary for maintaining conformation of the CDRs, (c) preparing a nucleic acid molecule encoding an immunoglobulin molecule comprising a variable domain where the variable domain CDRs are the CDRs of the preselected immunoglobulin molecule and wherein the variable domain framework regions are the avian framework regions with the proviso that one or more of the amino acid residue positions identified in (b) as having different amino acid residues in the avian immunoglobulin molecule variable domain as compared to the preselected immunoglobulin molecule variable domain, contain the amino acid residue present in the preselected immunoglobulin variable domain, and (d) expressing the nucleic acid molecule of (c) to produce an immunoglobulin molecule having a chimeric variable domain.

69. The method of claim 68 wherein the avian immunoglobulin molecule accumulates in a host cell at least about 0.15% total soluble protein.

70. The method of claim 68 wherein the avian immunoglobulin amino acid sequence comprises SEQ ID NO: 51.

71. The method of claim 68 wherein the amino acid residue position which are necessary for maintaining conformation of the CDRs of the preselected immunoglobulin molecule are determined by the methods of Kabat, Chothia and the contact method.

72. The method of claim 68 wherein the immunoglobulin having a chimeric variable domain is a VL, VH, **scFv**, diabody, triabody or tetrabody.

L25 ANSWER 2 OF 2 USPATFULL on STN
2003:225279 Stabilizing peptides, polypeptides and antibodies which include them.
Benvenuto, Eugeno, Roma, ITALY
Franconi, Rosella, Anguillara Sabazia, ITALY
Desiderio, Angiola, Anguillara Sabazia, ITALY
Tavladoraki, Paraskevi, Roma, ITALY
US 2003157090 A1 20030821
APPLICATION: US 2002-169351 A1 20021029 (10)
WO 2000-IT554 20001229
PRIORITY: IT 1999-RM803 19991230

DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A peptide characterized in comprising a sequence selected from the group conisting of the sequences reported in the annexed sequence listing from SEQ ID NO: 1 to SEQ ID N: 8, and in that included in a variable region of an antibody make said antibody soluble and stable in cytoplasm, the peptides comprising the sequences from SEQ ID NO: 1 to SEQ ID NO: 4 being included in the variable region of the heavy chain of an antibody, covalently linked to peptides comprising the sequences reported in the annexed sequence listing from SEQ ID NO: 88 to SEQ ID NO: 90 in the order SEQ ID NO:1-SEQ ID NO:88-SEQ ID NO:2-SEQ ID NO:89-SEQ ID NO:3-SEQ ID NO:90-SEQ ID NO:4, and the peptides comprising the sequences from SEQ ID NO: 5 to SEQ ID NO: 8 being included in the variable region of the light chain of an antibody, covalently linked to peptides comprising the sequences reported in the annexed sequence listing from SEQ ID NO: 91 to SEQ ID NO: 93 in the order SEQ ID NO:5-SEQ ID NO:91-SEQ ID NO:6-SEQ ID NO:92SEQ ID NO:7-SEQ ID NO:93-SEQ ID NO:8:

2. The peptide according to claim 1, wherein said peptide comprises the sequence reported in the annexed sequence listing as SEQ ID NO: 1, and Xaa in position 24 is Ala; said peptide comprises the sequence reported in the annexed sequence listing as SEQ ID NO: 2, and Xaa in position 12 is Leu; said peptide comprises the sequence reported in the annexed sequence listing as SEQ ID NO: 3, and Xaa in position 2 is Pro, Xaa in position 3 is Asp, Xaa in position 13 is Arg, Xaa in position 18 is Asn, and/or Xaa in position 20 is Leu; or said peptide comprises the sequence reported in the annexed sequence listing as SEQ ID NO: 7, and Xaa in position 12 is Arg, and/or Xaa in position 15, is Phe.

3. A process for preparing a polypeptide suitable as a variable region of an antibody stable and soluble in cytoplasm and specific for a **predetermined antigen** comprising the step of: producing an antibody having as a variable region of the heavy chain the polypeptide comprising the sequence reported in the sequence listing as SEQ ID NO: 101, and as a variable region of the light chain the polypeptide comprising the sequence reported in the annexed sequence listing as SEQ ID NO: 102; putting in contact said antibody with said antigen and selecting the antibody binding said antigen, isolating the polypeptide of the variable region of the heavy chain and/or the polypeptide of the variable region of the light chain of the antibody binding said antigen.

4. The process according to claim 3, futher comprising the step of sequencing the variable regions of said antibody binding said antigen.

5. The process according to claim 3 or 4, wherein said antigen is Tat, Rev, E7 or NS3 protein.

6. A polypeptide comprising the sequence reported in the annexed sequence listing as SEQ ID NO: 101 or SEQ ID NO: 102.

7. A polypeptide obtainable by the process according to claim 3.

8. The polypeptide according to claim 7, wherein said polypeptide comprises a sequence selected from the group consisting of the sequences reported in the sequence listing from SEQ ID NO:31 to SEQ ID NO: 48.

9. A process for producing a peptide conferring to an antibody binding specificity to a **predetermined antigen** comprising the step of: producing an antibody having as a variable region of the heavy chain the polypeptide comprising the sequence reported in the sequence listing as

SEQ ID NO: 101, and as a variable region of the light chain the polypeptide comprising the sequence reported in the annexed sequence listing as SEQ ID NO: 102; putting in contact said antibody with said antigen and selecting the antibody binding said antigen, isolating the polypeptide of the variable region of the heavy chain and/or the polypeptide of the variable region of the light chain of the antibody binding said antigen; isolating from said polypeptide the part conferring binding specificity to said antibody.

10. A peptide obtainable by the process according to claim 9.

11. The peptide according to claim 10 characterized by the fact of comprising a sequence selected from the group-consisting of the sequences reported in the annexed sequence listing from SEQ ID NO:9 to SEQ ID NO: 30 and as SEQ ID NO: 94.

12. An antibody characterized by the fact of including as a variable region of the heavy chain or as a variable region of the light chain the polypeptide according to claim 7.

13. An antibody according to claim 12 characterized by the fact of including as variable region of the heavy chain a polypeptide comprising the sequence reported in the annexed sequence listing as SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47, and respectively as variable region of the light chain a polypeptide comprising the sequences reported in the annexed sequence listing as SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, or SEQ ID NO:48.

14. An antibody according to claim 12, wherein said antibody is a **scFv**, FAB, Fv, dAb, IgG or IgA.

15. An antibody according to claim 13, wherein said antibody is a **scFv**, FAB, IgG or IgA.

16. An antibody according to claim 14 or 15, wherein said antibody is a **scFv** and the polypeptides included as variable regions of the heavy chain and of the light chain are connected by a linker.

17. An antibody according to claim 16, wherein said linker comprises the sequence reported in the annexed sequence listing in as SEQ ID NO: 51.

18. A process for obtaining an antibody according to any of claim 12 to 17, producing an antibody having as a variable region of the heavy chain the polypeptide having the sequence reported in the sequence listing as SEQ ID NO: 101, and as a variable region of the light chain the polypeptide having the sequence reported in the annexed sequence listing as SEQ ID NO: 102; putting in contact said antibody with said antigen and selecting the antibody binding said antigen.

19. A polynucleotide characterized by the fact of coding for a peptide according to any one of claims 1, 2, 10, and 11.

20. A polynucleotide characterized by the fact of coding for a polypeptide according to any of claims 6 to 8.

21. A polynucleotide according to claim 20, comprising a sequence selected from the group consisting of sequences reported in the annexed sequence listing as SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76,

SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94 and SEQ ID NO: 95.

22. A polynucleotide characterized by the fact of coding for an antibody according to any one of claims 12 to 17.

23. A polynucleotide according to claim 22, comprising a sequence selected from the group consisting of sequences reported in the annexed sequence listing as SEQ ID NO: 84 and SEQ ID NO: 69.

24. A pharmaceutical composition characterized by the fact of including as an active agent a therapeutically effective amount of an antibody according to any one of claims 12 to 17 together with a pharmaceutically acceptable carrier vehicle or auxiliary agent.

25. A pharmaceutical composition characterized by the fact of including as an active agent a therapeutically effective amount of the polynucleotides according to any one of claims 19 to 23 together with a pharmaceutically acceptable carrier vehicle or auxiliary agent.

26. The antibody according to any one of claims 12 to 17, for use as a medicament.

27. Use of the antibody according to any one of claims 12 to 17, for the manufacture of a medicament for the treatment of pathologies associated with accumulation of a molecule inside or outside a human, or animal cell.

28. A polynucleotide according to any one of the claims 25 to 29, for use as a medicament.

29. Use of the polynucleotide according to any one of the claims 19 to 23, for the manufacture of a medicament for the gene therapy of pathologies associated with the accumulation of a molecule inside or outside a human or animal cell.

30. Use of the antibodies according to any one of claims 12 to 17, and/or of the polynucleotides according to any one of claims 19 to 23, for the diagnosis of pathologies associated with the accumulation of a molecule inside or outside a human, animal or plant cell.

31. A diagnostic kit comprising as a reagent an antibody according to any of claims 12 to 17, and/or the polynucleotides according to any one of claims 19 to 23.

32. A diagnostic kit comprising as a reagent a peptide according to claim 10 or 11.

33. Use of an antibody according to any of claims 12 to 17 and/or of a polynucleotide according to claim 19 to 23 for the treatment of pathologies associated with the accumulation of a molecule inside or outside a plant cell.

=> d his

(FILE 'HOME' ENTERED AT 20:15:09 ON 27 SEP 2006)

FILE 'USPATFULL' ENTERED AT 20:15:17 ON 27 SEP 2006
E HUSTON JAMES S/IN

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L1            26 S E3
L2             7 S L1 AND (FRAMEWORK REGION?/CLM)
                 E OPPERMANN H/AU
                 E E12
L3           101 S E3-E5
L4            84 S L3 NOT L1
L5             0 S L4 AND (FRAMEWORK REGION?/CLM)

     FILE 'WPIDS' ENTERED AT 20:20:02 ON 27 SEP 2006
                 E HUSTON J S/IN
L6            20 S E3
L7             9 S L6 AND (FRAMEWORK REGION?)
                 E OPPERMANN H/IN
L8           138 S E3
L9           126 S L8 NOT L6
L10            0 S L9 AND (FRAMEWORK REGION?)

     FILE 'MEDLINE' ENTERED AT 20:23:24 ON 27 SEP 2006
                 E HUSTON J S/AU
L11           35 S E3
L12            0 S L11 AND (FRAMEWORK REGION?)
                 E OPPERMANN H/AU
L13           75 S E3
L14           65 S L13 NOT L11
L15            1 S L14 AND (FRAMEWORK)

     FILE 'USPATFULL' ENTERED AT 20:32:29 ON 27 SEP 2006
L16          380 S (FRAMEWORK REGION?/CLM)
L17          197 S L16 AND (COMPLEMENTARITY DETERMINING REGION?/CLM)
L18           17 S L17 AND LINKER/CLM
L19           11 S L18 NOT L1
L20           16 S (BIOSYNTHETIC ANTIBODY BINDING SITE?/CLM OR BABS/CLM)
L21           15 S L20 NOT L1
L22           15 S L21 NOT L19
L23         1098 S (SINGLE-CHAIN FV/CLM OR SCFV/CLM OR SFV/CLM)
L24            2 S L23 AND (PREDETERMINED ANTIGEN/CLM)
L25            2 S L24 NOT L1

=> file wpids
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              70.30     169.75

FILE 'WPIDS' ENTERED AT 20:38:30 ON 27 SEP 2006
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MOST RECENT DERWENT UPDATE:     200662        <200662/DW>
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=> s (framework region?)
         31820 FRAMEWORK
        437716 REGION?
L26        365 (FRAMEWORK REGION?)
                 (FRAMEWORK(W)REGION?)

=> s l26 and (complementarity determining region?)
          1372 COMPLEMENTARITY
        257753 DETERMINING
        437716 REGION?
           791 COMPLEMENTARITY DETERMINING REGION?
                 (COMPLEMENTARITY(W)DETERMINING(W)REGION?)
L27        187 L26 AND (COMPLEMENTARITY DETERMINING REGION?)

=> s l27 and linker
          9011 LINKER
L28         14 L27 AND LINKER

=> d his

     (FILE 'HOME' ENTERED AT 20:15:09 ON 27 SEP 2006)

     FILE 'USPATFULL' ENTERED AT 20:15:17 ON 27 SEP 2006
                E HUSTON JAMES S/IN
L1           26 S E3
L2            7 S L1 AND (FRAMEWORK REGION?/CLM)
                E OPPERMANN H/AU
                E E12
L3          101 S E3-E5
L4           84 S L3 NOT L1
L5            0 S L4 AND (FRAMEWORK REGION?/CLM)

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L6           20 S E3
L7            9 S L6 AND (FRAMEWORK REGION?)
                E OPPERMANN H/IN
L8          138 S E3
L9          126 S L8 NOT L6
L10           0 S L9 AND (FRAMEWORK REGION?)

     FILE 'MEDLINE' ENTERED AT 20:23:24 ON 27 SEP 2006
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L11          35 S E3
L12           0 S L11 AND (FRAMEWORK REGION?)
                E OPPERMANN H/AU
L13          75 S E3
L14          65 S L13 NOT L11
L15           1 S L14 AND (FRAMEWORK)

     FILE 'USPATFULL' ENTERED AT 20:32:29 ON 27 SEP 2006
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L17         197 S L16 AND (COMPLEMENTARITY DETERMINING REGION?/CLM)
L18          17 S L17 AND LINKER/CLM
L19          11 S L18 NOT L1
L20          16 S (BIOSYNTHETIC ANTIBODY BINDING SITE?/CLM OR BABS/CLM)
L21          15 S L20 NOT L1
L22          15 S L21 NOT L19
L23        1098 S (SINGLE-CHAIN FV/CLM OR SCFV/CLM OR SFV/CLM)
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L24             2 S L23 AND (PREDETERMINED ANTIGEN/CLM)
L25             2 S L24 NOT L1

     FILE 'WPIDS' ENTERED AT 20:38:30 ON 27 SEP 2006
L26           365 S (FRAMEWORK REGION?)
L27           187 S L26 AND (COMPLEMENTARITY DETERMINING REGION?)
L28            14 S L27 AND LINKER

=> s l28 not l6
L29            7 L28 NOT L6

=> d l29,bib,ab,1-7

L29  ANSWER 1 OF 7  WPIDS  COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN   2006-020522 [02]   WPIDS
DNC  C2006-006194
TI   New T-cell receptor (TCR) comprises at least one TCR alpha chain variable
     domain and/or at least one TCR beta chain variable domain, useful for
     treating cancer.
DC   B04 D16
IN   JAKOBSEN, B K; LI, Y
PA   (AVID-N) AVIDEX LTD
CYC  109
PI   WO 2005116075   A1 20051208 (200602)* EN  156
        RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT
            KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG
            ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE
            DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
            KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ
            OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA
            UG US UZ VC VN YU ZA ZM ZW
ADT  WO 2005116075 A1 WO 2005-GB970 20050315
PRAI GB 2004-19644        20040903; GB 2004-11772        20040526
AB   WO2005116075 A UPAB: 20060106
     NOVELTY - A T-cell receptor (TCR) having the property of binding to HLA-A
     asterisk 0201 and comprises at least one TCR alpha chain variable domain
     and/or at least one TCR beta chain variable domain, is new.
          DETAILED DESCRIPTION - A T-cell receptor (TCR) having the property of
     binding to Ile-Leu-Ala-Lys-Phe-Leu-His-Trp-Leu-HLA-A asterisk 0201 and
     comprising at least one TCR alpha chain variable domain and/or at least
     one TCR beta chain variable domain, where the TCR has a KD for the
     Ile-Leu-Ala-Lys-Phe-Leu-His-Trp-Leu-HLA-A asterisk 0201 complex of less
     than or equal to 1 mu M and/or has an off-rate (koff) for the
     Ile-Leu-Ala-Lys-Phe-Leu-His-Trp-Leu-HLA-A asterisk 0201 complex of 1x10-3
     S-1 or slower, is new.
          INDEPENDENT CLAIMS are also included for:
          (1) a soluble TCR comprising the alpha chain amino acid sequence
     comprising fully defined 205 amino acids (SEQ ID NO. 71) and one of 6 beta
     chain amino acid sequences comprising fully defined 243 amino acids (SEQ
     ID NO. 73-78);
          (2) a multivalent TCR complex comprising at least two TCRs above, and
     linked by a non-peptidic polymer chain or a peptidic linker sequence;
          (3) an isolated cell presenting a TCR above;
          (4) a pharmaceutical composition comprising a TCR or a multivalent
     TCR complex, or cells above, and a carrier;
          (5) treating cancer; and
          (6) producing a high affinity TCR.
          ACTIVITY - Cytostatic.
          No biological data is given.
          MECHANISM OF ACTION - Gene Therapy.
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USE - The TCR, multivalent TCR complex, or cells above are useful in the preparation of a composition for the treatment of cancer (claimed). The TCR and the multivalent TCR complex are useful for treating cancer. Dwg.0/21

L29 ANSWER 2 OF 7 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2006-020043 [02] WPIDS
DNC C2006-005970
TI Novel T-Cell receptor that binds to peptide derived from NY-ESO-1 protein and comprising TCR alpha chain variable domain and/or TCR beta chain variable domain, useful for preparing composition for treatment of cancer.
DC A96 B04 D16
IN BOULTER, J M; DUNN, S M; JAKOBSEN, B K; LI, Y; MOLLOY, P E
PA (AVID-N) AVIDEX LTD
CYC 111
PI WO 2005113595 A2 20051201 (200602)* EN 110
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT WO 2005113595 A2 WO 2005-GB1924 20050518
PRAI GB 2004-19643 20040903; GB 2004-11123 20040519
AB WO2005113595 A UPAB: 20060106
NOVELTY - A T-Cell receptor (TCR) (I) having the property of binding to a peptide derived from NY-ESO-1 protein and comprising at least one TCR alpha chain variable domain and/or at least one TCR beta chain variable domain, where the TCR has a KD for NY-ESO-1 protein of less than or equal to 1 and/or has an off-rate (k(off) for NY-ESO-1 protein of 1x10-3 S-1 or slower, is new.

DETAILED DESCRIPTION - A T-Cell receptor (TCR) having the property of binding to Ser-Leu-Leu-Met-Trp-Ile-Thr-Gln-Cys-HLA-A asterisk 0201 and comprising at least one TCR alpha chain variable domain and/or at least one TCR beta chain variable domain, where the TCR has a KD for the Ser-Leu-Leu-Met-Trp-Ile-Thr-Gln-Cys-HLA-A asterisk 0201 complex of less than or equal to 1 and/or has an off-rate (k(off) for Ser-Leu-Leu-Met-Trp-Ile-Thr-Gln-Cys-HLA-A asterisk 0201 complex of 1x10-3 S-1 or slower.

INDEPENDENT CLAIMS are also included for:

(1) a soluble TCR (II) consisting of the alpha chain amino acid sequence having SEQ ID No. 122 and beta chain amino acid sequence having SEQ ID No. 123 or 124;

(2) a multivalent TCR complex (III) comprising at least two TCRs of (I) or (II), linked by a non-peptidic polymer chain or a peptide **linker** sequence;

(3) a multivalent TCR complex (IV) comprising at least two TCRs at least one of (I), where at least one of the TCR is associated with a therapeutic agent described in (II);

(4) an isolated cell (V) presenting (I);

(5) a pharmaceutical composition (PC1) comprising a TCR or a multivalent TCR complex of (I) or several cells of (V), together with a carrier;

(6) treating (M1) of cancer, involves administering to a subject suffering such cancer an effective amount of a TCR or a multivalent TCR complex of (I) or (V); and

(7) producing a high affinity TCR having the property of binding to Ser-Leu-Leu-Met-Trp-Ile-Thr-Gln-Cys-HLA-A asterisk 0201, where the TCR comprises at least one TCR alpha chain variable domain and/or at least one TCR beta chain variable domain and has a KD for the Ser-Leu-Leu-Met-Trp-

Ile-Thr-Gln-Cys-HLA-A asterisk 0201 complex of less than 1 mu M and/or an off-rate (k(off) for Ser-Leu-Leu-Met-Trp-Ile-Thr-Gln-Cys-HLA-A asterisk 0201 complex of less than 1x10-3, involves producing a TCR comprising the alpha and beta chain variable domain of the 1G4 TCR, where one or both of the alpha and beta chain variable domains comprise a mutation(s) in one or more of the amino acids identified in (I), contacting the mutated TCR with Ser-Leu-Leu-Met-Trp-Ile-Thr-Gln-Cys-HLA-A asterisk 0201 under conditions suitable to allow the binding of the TCR to Ser-Leu-Leu-Met-Trp-Ile-Thr-Gln-Cys-HLA-A asterisk 0201 and measuring the KD and/or k(off) of the interaction.

ACTIVITY - Cytostatic.

Fifty female nude mice were injected subcutaneously with the human melanoma tumor forming cell line (SK-MEL-37) which had been stably transfected with a NY-ESO peptide/ubiquitin minigene construct in ensure enhanced expression of the class I-peptide target at the cell surface. Tumors were allowed to grow in the animals for 5 days to allow tumor development prior to commencement of treatment. The rats then received the following intravenous bolus dosage of c58c61 high affinity NY-ESO TCR/IL-2 fusion protein. Doses ranged between 0.02 and 1.0 mg/kg high affinity 1G4 TCR/IL-2 fusion proteins in phosphate buffered saline (PBS), administered at 5-8, 11, 13, 17, 20, 24,28, and 30 day post-tumor engraftment. In all experiments, a control treatment group was included where PBS alone was substituted for the TCR/IL-2 immunoconjugate. Tumor size was then measured using calipers and tumor volume was determined. Results showed that TCR/IL-2 immunoconjugate exhibited a clear dose-dependent anti-tumor effect.

MECHANISM OF ACTION - None given.

USE - (I)-(III) is useful for preparing a composition for the treatment of cancer. (M1) is useful for treating cancer (claimed).

Dwg.0/22

L29 ANSWER 3 OF 7 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 2004-420275 [39] WPIDS

DNC C2004-157827

TI New proteinaceous particle (e.g. bacteriophage or ribosome) displaying on its surface a T-cell receptor (TCR), useful for treating HTLV-I infection or cancer or for identifying modulators of TCR-mediated cellular immune synapse.

DC B04 D16

IN ANDERSEN, T B; BOULTER, J M; JAKOBSEN, B K; LI, Y; MOLLOY, P E; ANDERSEN, T

PA (AVID-N) AVIDEX LTD

CYC 104

PI WO 2004044004 A2 20040527 (200439)* EN 204

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

AU 2003276403 A1 20040603 (200470)

EP 1558643 A2 20050803 (200551) EN

R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR

NO 2005002743 A 20050808 (200558)

CN 1714102 A 20051228 (200636)

ADT WO 2004044004 A2 WO 2003-GB4636 20031030; AU 2003276403 A1 AU 2003-276403 20031030; EP 1558643 A2 EP 2003-811009 20031030, WO 2003-GB4636 20031030; NO 2005002743 A WO 2003-GB4636 20031030, NO 2005-2743 20050608; CN 1714102 A CN 2003-80102928 20031030

FDT AU 2003276403 A1 Based on WO 2004044004; EP 1558643 A2 Based on WO 2004044004

PRAI GB 2003-16356 20030711; GB 2002-26227 20021109;
GB 2003-1814 20030125; GB 2003-4067 20030222;
US 2003-463046P 20030416; GB 2003-11397 20030516

AB WO2004044004 A UPAB: 20060612

NOVELTY - A proteinaceous particle displaying on its surface a T-cell receptor (TCR), is new.

DETAILED DESCRIPTION - The proteinaceous particle is characterized in that:

(a) the proteinaceous particle is a ribosome and the TCR is a single chain TCR (scTCR) polypeptide, or dimeric TCR (dTCR) polypeptide pair;

(b) the proteinaceous particle is a filamentous phage particle, or a cell with cell surface protein or polypeptide molecules to which the TCR is covalently linked, and the TCR is a human scTCR or a human dTCR polypeptide pair;

(c) the proteinaceous particle is a phage particle, or a cell with cell surface protein or polypeptide molecules to which the TCR is covalently linked, and the TCR is a non-human dTCR polypeptide pair; or

(d) the proteinaceous particle is a phage particle, or a cell with cell surface protein or polypeptide molecules to which the TCR is covalently linked, and the TCR is a scTCR polypeptide comprising TCR amino acid sequences corresponding to extracellular constant and variable domain sequences present in native TCR chains and a **linker** sequence, the latter linking a variable domain sequence corresponding to that of one chain of a native TCR to a constant domain sequence corresponding to a constant domain sequence of another native TCR chain, and a disulfide bond which has no equivalent in native T-cell receptors links residues of the constant domain sequences.

INDEPENDENT CLAIMS are also included for the following:

(1) a diverse library of dTCR polypeptide pairs or scTCR polypeptides displayed on proteinaceous particles the dTCR polypeptide pairs or scTCR polypeptides having the structural features cited above;

(2) a nucleic acid encoding one chain of a dTCR polypeptide pair and the other chain of a dTCR polypeptide pair fused to a nucleic acid sequence encoding a protein capable of forming part of the surface of a proteinaceous particle; or nucleic acid encoding a scTCR polypeptide fused to a nucleic acid sequence encoding a protein capable of forming part of the surface of a proteinaceous particle, the dTCR pair or scTCR having the structural features cited above;

(3) an expression vector comprising the above nucleic acid, or a composition comprising a first vector comprising the above nucleic acid and a second vector comprising the above nucleic acid;

(4) an expression system comprising phagemid or phage genome vectors expressing the nucleic acid cited above;

(5) a host cell comprising the above nucleic acid, expression vector or expression system;

(6) a method for identifying TCRs with a specific characteristic;

(7) a method for detecting TCR ligand complexes;

(8) a method of identifying an inhibitor of the interaction between the TCR-displaying proteinaceous particle(s) and a TCR-binding ligand;

(9) a TCR specific for a given TCR ligand, which has the structural features cited above, is mutated in the variable domain(s) relative to the native TCR specific for the TCR ligand and which has a Kd or an off-rate (koff) for the TCR ligand less than that of the native TCR as measured by Surface Plasmon Resonance;

(10) a nucleic acid encoding the TCR in (9); and

(11) methods of treating HTLV-1 infection or cancer.

ACTIVITY - Virucide; Cytostatic.

No biological data given.

MECHANISM OF ACTION - T-cell Receptor therapy.

USE - For the identification of high affinity TCRs or in identifying

modulators, including inhibitors, of the TCR-mediated cellular immune synapse. The TCR is used in preparing a composition for the treatment of HTLV-I infection or cancer (claimed).
Dwg.0/0

L29 ANSWER 4 OF 7 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2003-636673 [60] WPIDS
DNC C2003-174064
TI Antibody targeting compound useful e.g. for diagnostic immunoassays and treating microbial diseases comprises targeting or biological agent covalently linked to combining site of the antibody.
DC B04 B05 D16
IN BARBAS, C F; LERNER, R; RADER, C; SINHA, S C; LERNER, R A
PA (SCRI) SCRIPPS RES INST
CYC 102
PI WO 2003059251 A2 20030724 (200360)* EN 56
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2003175921 A1 20030918 (200362)
US 2003190676 A1 20031009 (200367)
AU 2002365182 A1 20030730 (200421)
EP 1443963 A2 20040811 (200452) EN
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
KR 2004058229 A 20040703 (200472)
JP 2005514430 W 20050519 (200538) 60
CN 1606454 A 20050413 (200554)
ADT WO 2003059251 A2 WO 2002-US33991 20021022; US 2003175921 A1 Provisional US 2001-344614P 20011022, Provisional US 2002-412455P 20020919, US 2002-278364 20021022; US 2003190676 A1 Provisional US 2001-344614P 20011022, Provisional US 2002-412455P 20020919, Cont of US 2002-278364 20021022, US 2003-420373 20030421; AU 2002365182 A1 AU 2002-365182 20021022; EP 1443963 A2 EP 2002-804108 20021022, WO 2002-US33991 20021022; KR 2004058229 A KR 2004-706008 20040422; JP 2005514430 W WO 2002-US33991 20021022, JP 2003-559416 20021022; CN 1606454 A CN 2002-825631 20021022
FDT AU 2002365182 A1 Based on WO 2003059251; EP 1443963 A2 Based on WO 2003059251; JP 2005514430 W Based on WO 2003059251
PRAI US 2002-412455P 20020919; US 2001-344614P 20011022;
US 2002-278364 20021022; US 2003-420373 20030421
AB WO2003059251 A UPAB: 20030919
NOVELTY - An antibody-targeting compound comprises at least one targeting agent and/or at least one biological agent. The agents are covalently linked to the combining site of the antibody.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) production of antibody targeting compound involving covalently linking the targeting agents and/or biological agents to combining site of antibody;
(2) modifying antibody which exhibits low or non-detectable binding affinity for particular target molecule to increase binding specificity of antibody for particular target molecule, involving covalently linking targeting agents or biological agents specific for target molecule to combining site of antibody to generate antibody targeting compound;
(3) altering at least one biological characteristic of targeting agent or biological agent involving covalently linking targeting or biological agent to the combining site of antibody, where covalent linking

alters at least one biological characteristic of targeting or biological agent;

(4) agent-**linker** compound (C1) for covalently linking to combining site of antibody comprising at least one targeting and/or biological agent, where **linker** is of formula X-Y-Z1 (I);

(5) agent-**linker**-antigen compound (C2) for non-covalently linking to combining site of antibody, where (C2) comprising at least two targeting agents other than antibody and/or at least two biological agents, is covalently linked via **linker** to antigen recognized by antibody and **linker** is a linear or branched (preferably branched) connecting chain of atoms comprising any of C, H, N, O, P, S, Si, F, Cl, Br, and I, or their salt;

(6) antibody targeting compound comprising (C1) covalently or (C2) non-covalently associated with combining site of antibody specific for antigen;

(7) modifying binding specificity of antibody specific for antigen involving contacting antibody with (C2) where antibody acquires binding specificity of targeting or biological agent;

(8) imaging cells or tissue expressing target molecule in individual involving administration of (C1) linked to detectable label or separate administration of (C2) linked to label so that (C2) non-covalently associates with antibody combining site in vivo;

(9) screening chemical library for agonists or antagonists of receptor, involving covalently linking individual members of chemical library to combining site of antibody and then testing antibody linked library for binding to receptor or for inhibition of binding between receptor and ligand for receptor (preferably by detecting cellular signal resulting from binding or inhibition of binding);

(10) determining amount of analyte from sample in immunoassay involving:

(a) forming complex between analyte and at least one antibody specific for the analyte, in medium containing the sample;

(b) analyzing medium for complex; and

(c) relating amount of complex to amount of analyte in sample, where improvement in analysis involves forming complex with at least one antibody targeting compound specific for analyte, and non-antibody targeting agent or biological agent specific for analyte, covalently linked to combining site of antibody provides the specificity;

(11) delivering biological activity to cells, tissue extracellular matrix biomolecule or a biomolecule in fluid of individual, involving separate administration of (C2) and antibody specific for antigen, where (C2) associates non-covalently with the antibody in vivo and is specific for cells or biomolecules;

(12) treating or preventing a disease or condition in which cells, tissue or fluid expresses a target molecule, involving separately administering (C2) and antibody specific for antigen, where (C2) non-covalently associates in vivo with antibody;

(13) mediating intracellular delivery of intracellularly active drug involving:

(a) preparing antibody targeting compound comprising at least one targeting agent and/or biological agent covalently linked via **linker** to the combining site of the antibody, where targeting or biological agent binds to cell receptor and mediates internalization and targeting compound also comprises drug that becomes active intracellularly; and

(b) contacting cell with antibody targeting compound of step (a) to induce internalization of antibody targeting agent and intracellular delivery of drug; and

(14) modifying physical or biological property of antibody targeting compound involving:

(a) preparing antibody targeting compound comprising antibody to which at least one targeting or biological agent has been covalently linked via **linker** through combining site of antibody;

(b) modifying at least one chemical characteristic of **linker**; and

(c) determining if physical or biological property of antibody targeting compound has been modified.

X = a linear or branched connecting chain of atoms comprising any of C, H, N, O, P, S, Si, halo or their salts;

Y = a single or fused 5 or 6 membered homo- or hetero-carbocylic optionally saturated ring; and

Z1 = reactive group (preferably ketone, diketone, beta lactam, active ester, haloketone, lactone, anhydride, epoxide, aldehyde, maleimide disulfide, or aryl halide) for covalently linking the agent to a side chain of a reactive amino acid in the combining site of the antibody.

ACTIVITY - Antimicrobial; Virucide.

In in vitro assays, targeted antibodies were shown to have increased potency in inhibiting HIV-1 entry and infection.

MECHANISM OF ACTION - None given.

USE - The method is used for targeting antibody; for modifying binding specificity of an antibody which exhibits low or non-detectable binding affinity for a particular target molecule; for altering biological characteristics of antibody; for delivering a biological activity to cells, tissue extracellular matrix or fluid biomolecules; for treating and preventing a disease or condition involving expression of the target molecule by cells, tissues or fluid; for imaging cells or extracellular matrix expressing the target molecule; for reducing infectivity of microbial cells and viral particles; in immunoassays for detecting and measuring analyte in a sample; for mediating intracellular delivery of prodrugs which are activated intracellularly; for reducing the ability of a cell penetrating targeting agent or biological agent to cross the cell membrane (all claimed).

ADVANTAGE - The antibody targeting compounds improve valency, potency and half-life of the biological agents. The antigen binding specificity of the antibody before covalent linkage is optionally substantially modified following covalent linkage. The antibody prior to covalent linking exhibits an affinity for the particular target molecule of less than 1 multiply 10-5 moles/liter and after linking exhibits an affinity of greater than 1 multiply 10-6 moles/liter. The binding of the targeting agent to the antibody improves and alters physical as well as biological properties of the antibody.

Dwg.0/14

L29 ANSWER 5 OF 7 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 2003-371805 [35] WPIDS

DNC C2003-098653

TI New immunoglobulin molecule, useful in therapeutic or diagnostic assays comprising ELISA, phage display, tumor imaging or protein chips assay or in screening assays for detecting molecules that bind to the immunoglobulin molecule.

DC B04 D16

IN DI FIORE, S; EMANS, N; FISCHER, R; SCHILLBERG, S; ZHANG, M Y; ZIMMERMANN, S; FIORE, S D; ZHANG, M

PA (FRAU-N) FRAUNHOFER INST MOLEKULARBIOLOGIE ANGE; (FRAU) FRAUNHOFER GES FOERDERUNG ANGEWANDTEN EV; (EMAN-I) EMANS N; (FIOR-I) FIORE S D; (FISC-I) FISCHER R; (SCHI-I) SCHILLBERG S; (ZHAN-I) ZHANG M; (ZIMM-I) ZIMMERMANN S

CYC 101

PI WO 2003025124 A2 20030327 (200335)* EN 198

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

EP 1434800 A2 20040707 (200444) EN
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
AU 2002324973 A1 20030401 (200452)
US 2005037420 A1 20050217 (200514)
AU 2002324973 A8 20051020 (200615)
ADT WO 2003025124 A2 WO 2002-US29003 20020913; EP 1434800 A2 EP 2002-759649 20020913, WO 2002-US29003 20020913; AU 2002324973 A1 AU 2002-324973 20020913; US 2005037420 A1 Provisional US 2001-318904P 20010914, WO 2002-US29003 20020913, US 2004-489328 20040827; AU 2002324973 A8 AU 2002-324973 20020913
FDT EP 1434800 A2 Based on WO 2003025124; AU 2002324973 A1 Based on WO 2003025124; AU 2002324973 A8 Based on WO 2003025124
PRAI US 2001-318904P 20010914; US 2004-489328 20040827
AB WO2003025124 A UPAB: 20030603
NOVELTY - Immunoglobulin molecule comprising:

(a) one or more heavy chain **framework regions** comprising HFR1, HFR2, HFR3 or HFR4 and one or more light chain **framework regions** comprising LFR1, LFR2, LFR3 or LFR4; and

(b) **complementarity determining regions** (CDRs) comprising CDR-H1, CDR-H2, CDR-H3 and/or CDRL1, CDR-L2 or CDR-L3, is new.

DETAILED DESCRIPTION - The immunoglobulin molecule has the structure:

(i) HFR1-CDR-H1-HFR2-CDR-H2-HFR3-CDR-H3-HFR4; or

(ii) LFR1-CDR-L1-LFR2-CDR-L2-LFR3-CDR-L3-LFR4.

The length of, and positions of the amino acid residues in, the CDRs and the **framework regions** are in accordance with the Kabat numbering system. HFR1 is a first **framework region** in (B) comprising a sequence of about 30 amino acid residues. HFR2 is a second **framework region** in (B) comprising a sequence of about 14 amino acid residues. HFR3 is a third **framework region** in (B) comprising a sequence of about 29-32 amino acid residues. HFR4 is a **framework region** in (B) comprising a sequence of 7-9 amino acid residues, where the first amino acid is tryptophan (Trp). CDR-H1 is a first complementary determining region. CDR-H2 is a second complementary determining region. CDR-H3 is a third complementary determining region. LFR1 is a first **framework region** comprising a sequence of about 22-23 amino acid residues. LFR2 is a second **framework region** comprising a sequence of about 13-16 amino acid residues, where a Pro or Leu must be at position 10 if the sequence is 15 amino acid residues long or position 11 if the sequence is 16 amino acid residues long. LFR3 is a third **framework region** comprising a sequence of about 32 amino acid residues. LFR4 is a fourth **framework region** comprising a sequence of about 12-13 amino acid residues, where the first amino acid residue is Phe. CDR-L1 is a first complementary determining region. CDR-L2 is a second complementary determining region. CDR-L3 is a third complementary determining region.

INDEPENDENT CLAIMS are also included for:

(1) a composition comprising the immunoglobulin molecule;

(2) a population of isolated immunoglobulin molecules;

(3) an isolated nucleic acid molecule encoding the immunoglobulin molecule;

(4) a recombinant library comprising one or more the nucleic acid molecule;

(5) a vector comprising the nucleic acid molecule in operable linkage with a promoter;

(6) a host cell comprising the nucleic acid molecule;

(7) generating a recombinant library of nucleic acid molecules encoding the immunoglobulin molecules having identical **framework regions** and accumulating to high levels in a host cell;

(8) producing a plant resistant to a pathogen;

(9) preparing the recombinant library expressing immunoglobulin molecules or their domains;

(10) identifying an immunoglobulin molecule of the recombinant

library that binds to a predetermined antigen;
(11) preparing a transgenic plant;
(12) a transgenic plant or its seed; and
(13) producing an immunoglobulin molecule having a chimeric variable domain.
USE - The immunoglobulin is useful in therapeutic or diagnostic assays comprising ELISA, phage display, tumor imaging or protein chips assay. Further, the immunoglobulin is useful in screening assays for detecting molecules that bind to the immunoglobulin molecule (claimed). Dwg.0/11

L29 ANSWER 6 OF 7 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2002-292258 [33] WPIDS
DNC C2002-085913
TI New polypeptide that binds endoglin, useful for diagnosis and treatment of tumors, is synthetic single-chain antibody.
DC B04 D16
IN KONTERMANN, R; MILLER, D; MUELLER, R; MULLER, R
PA (VECT-N) VECTRON THERAPEUTICS IMT AG; (VECT-N) VECTRON THERAPEUTICS AG; (KONT-I) KONTERMANN R; (MILL-I) MILLER D; (MULL-I) MULLER R
CYC 23
PI WO 2002020614 A2 20020314 (200233)* GE 37
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
W: CA JP US
DE 10043481 A1 20020411 (200233)
EP 1315760 A2 20030604 (200337) GE
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
JP 2004508035 W 20040318 (200420) 80
US 2004053329 A1 20040318 (200421)
ADT WO 2002020614 A2 WO 2001-EP10197 20010904; DE 10043481 A1 DE 2000-10043481 20000904; EP 1315760 A2 EP 2001-980336 20010904, WO 2001-EP10197 20010904; JP 2004508035 W WO 2001-EP10197 20010904, JP 2002-525233 20010904; US 2004053329 A1 WO 2001-EP10197 20010904, US 2003-363349 20030801
FDT EP 1315760 A2 Based on WO 2002020614; JP 2004508035 W Based on WO 2002020614
PRAI DE 2000-10043481 20000904
AB WO 200220614 A UPAB: 20020524
NOVELTY - A polypeptide (I) that binds specifically to the extracellular domain of human endoglin (CD105) comprising at least one fully defined sequence (S1) as given in the specification or its variant, is new.
DETAILED DESCRIPTION - A polypeptide (I) that binds specifically to the extracellular domain of human endoglin (CD105) comprising at least one fully defined sequence Arg-Thr-Thr-His-Gly-Pro-Asp-Pro-His (S1) as given in the specification or its variant, is new.
INDEPENDENT CLAIMS are also included for the following:
(a) nucleic acid (II) that encodes (I);
(b) vector containing at least one (II);
(c) cell containing at least one (II) or the vector of (b);
(d) recombinant production of (I); and
(e) pharmaceutical or diagnostic composition containing at least one (I), (II) and/or the vector of (b), optionally also auxiliaries or additives.
ACTIVITY - Cytostatic. No details of tests for cytostatic activity are given.
MECHANISM OF ACTION - Binding to, and neutralizing, CD105, a member of the transforming growth factor beta protein family that is overexpressed on tumoral endothelial cells.
USE - (I) is used for in vivo or in vitro detection of CD105 or cells, or their fragments, that express CD105 and to bind to CD105-expressing cancer cells to produce a cytotoxic effect, i.e. functioning as carrier for active agents such as adenoviruses or cytotoxic

T lymphocytes. Especially (I), also nucleic acid that encodes it and related vectors, are used for diagnosis and therapy of diseases associated with hyperproliferation of CD105+ cells, especially tumors.

ADVANTAGE - (I) do not induce a neutralizing human anti-mouse antibody response, and when they can also bind selectively to adenoviral vectors, they significantly improve viral transduction of target cells.

Dwg.0/1

L29 ANSWER 7 OF 7 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 1994-200254 [24] WPIDS

DNC C1994-091554

TI New ligand variable binding domains of reduced size - contain **complementarity determining regions** and **framework region** to provide correct orientation, also related DNA, expression vectors etc., useful for radio-imaging and tumour treatment.

DC B04 D16

IN SLATER, A M; TIMMS, D

PA (ZENE) ZENECA LTD; (ASTR) ASTRAZENECA AB

CYC 26

PI WO 9412625 A2 19940609 (199424)* EN 187
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA FI GB JP KR NO NZ RU
ZA 9308677 A 19940727 (199432) 187
AU 9455303 A 19940622 (199436)
WO 9412625 A3 19940721 (199517)
GB 2287247 A 19950913 (199540) 1
EP 673417 A1 19950927 (199543) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
GB 2287247 B 19960814 (199636)
EP 673417 B1 20030611 (200346) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
DE 69333044 E 20030717 (200355)

ADT WO 9412625 A2 WO 1993-GB2375 19931119; ZA 9308677 A ZA 1993-8677 19931119; AU 9455303 A AU 1994-55303 19931119; WO 9412625 A3 WO 1993-GB2375 19931119; GB 2287247 A WO 1993-GB2375 19931119, GB 1995-9600 19950511; EP 673417 A1 WO 1993-GB2375 19931119, EP 1994-900226 19931119; GB 2287247 B WO 1993-GB2375 19931119, GB 1995-9600 19950511; EP 673417 B1 WO 1993-GB2375 19931119, EP 1994-900226 19931119; DE 69333044 E DE 1993-633044 19931119, WO 1993-GB2375 19931119, EP 1994-900226 19931119

FDT AU 9455303 A Based on WO 9412625; GB 2287247 A Based on WO 9412625; EP 673417 A1 Based on WO 9412625; GB 2287247 B Based on WO 9412625; EP 673417 B1 Based on WO 9412625; DE 69333044 E Based on EP 673417, Based on WO 9412625

PRAI GB 1992-24588 19921123; GB 1992-27189 19921231

AB WO 9412625 A UPAB: 19940803

New ligand-binding variable domain (V-min.) comprises (A) a **framework region** of (a) cyclically permuted central beta-barrel, (b) outer beta-sheet segment and (c) **linker** sections, and (B) **complementarity determining regions** (CDR). The beta-barrel (opt. in conjunction with beta-sheet segments) orients the CDR in space for binding of ligand, while the **linker** sections form (A) to (B). The **framework region** itself has upto 180 amino acids.

USE/ADVANTAGE - V-min., opt. when conjugated, are useful in radioimaging, as immunotoxins and in antibody directed enzyme prodrug therapy, i.e. for diagnosis and treatment of tumours. Compared with ordinary antibodies, V-min are significantly smaller (as few as 160 amino acids), so may show improved tissue penetration and faster clearance from the body. Small size should also facilitate conjugation and oligomerisation. V-min can be expressed as a continuous polypeptide from a single gene.

Dwg.32/48

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=> d his

     (FILE 'HOME' ENTERED AT 20:15:09 ON 27 SEP 2006)

     FILE 'USPATFULL' ENTERED AT 20:15:17 ON 27 SEP 2006
                E HUSTON JAMES S/IN
L1           26 S E3
L2            7 S L1 AND (FRAMEWORK REGION?/CLM)
                E OPPERMANN H/AU
                E E12
L3          101 S E3-E5
L4           84 S L3 NOT L1
L5            0 S L4 AND (FRAMEWORK REGION?/CLM)

     FILE 'WPIDS' ENTERED AT 20:20:02 ON 27 SEP 2006
                E HUSTON J S/IN
L6           20 S E3
L7            9 S L6 AND (FRAMEWORK REGION?)
                E OPPERMANN H/IN
L8          138 S E3
L9          126 S L8 NOT L6
L10           0 S L9 AND (FRAMEWORK REGION?)

     FILE 'MEDLINE' ENTERED AT 20:23:24 ON 27 SEP 2006
                E HUSTON J S/AU
L11          35 S E3
L12           0 S L11 AND (FRAMEWORK REGION?)
                E OPPERMANN H/AU
L13          75 S E3
L14          65 S L13 NOT L11
L15           1 S L14 AND (FRAMEWORK)

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L16         380 S (FRAMEWORK REGION?/CLM)
L17         197 S L16 AND (COMPLEMENTARITY DETERMINING REGION?/CLM)
L18          17 S L17 AND LINKER/CLM
L19          11 S L18 NOT L1
L20          16 S (BIOSYNTHETIC ANTIBODY BINDING SITE?/CLM OR BABS/CLM)
L21          15 S L20 NOT L1
L22          15 S L21 NOT L19
L23        1098 S (SINGLE-CHAIN FV/CLM OR SCFV/CLM OR SFV/CLM)
L24           2 S L23 AND (PREDETERMINED ANTIGEN/CLM)
L25           2 S L24 NOT L1

     FILE 'WPIDS' ENTERED AT 20:38:30 ON 27 SEP 2006
L26         365 S (FRAMEWORK REGION?)
L27         187 S L26 AND (COMPLEMENTARITY DETERMINING REGION?)
L28          14 S L27 AND LINKER
L29           7 S L28 NOT L6

=> file medline
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              69.77     239.52

FILE 'MEDLINE' ENTERED AT 20:44:39 ON 27 SEP 2006

 FILE LAST UPDATED: 27 Sep 2006 (20060927/UP). FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.
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 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s (framework region?)
         51347 FRAMEWORK
        802979 REGION?
L30        415 (FRAMEWORK REGION?)
                 (FRAMEWORK(W)REGION?)

=> s l30 and (complementarity determining region? or CDR?)
          4959 COMPLEMENTARITY
        114822 DETERMINING
        802979 REGION?
          2329 COMPLEMENTARITY DETERMINING REGION?
                 (COMPLEMENTARITY(W)DETERMINING(W)REGION?)
          4415 CDR?
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=> s l31 and (single-chain or sFv)
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        409656 CHAIN
          5438 SINGLE-CHAIN
                 (SINGLE(W)CHAIN)
          1043 SFV
L32         11 L31 AND (SINGLE-CHAIN OR SFV)

=> d l32,cbib,ab,1-11

L32  ANSWER 1 OF 11     MEDLINE on STN
2005002129.    PubMed ID: 15627607.   Humanization of a chicken anti-IL-12
     monoclonal antibody. Tsurushita Naoya; Park Minha; Pakabunto Kanokwan; Ong
     Kelly; Avdalovic Anamarija; Fu Helen; Jia Audrey; Vasquez Max; Kumar
     Shankar. (Protein Design Labs, Inc., 34801 Campus Drive, Fremont, CA
     94555, USA.. ntsurushita@pdl.com) . Journal of immunological methods,
     (2004 Dec) Vol. 295, No. 1-2, pp. 9-19.  Journal code: 1305440. ISSN:
     0022-1759. Pub. country: Netherlands. Language: English.
AB   Chicken anti-IL-12 monoclonal antibodies were isolated by phage display
     using spleen cells from a chicken immunized with human and mouse IL-12 as
     a source for library construction.  One of the chicken monoclonal
     antibodies, DD2, exhibited binding to both human and mouse IL-12 in the
     single-chain Fv form and also after conversion to chicken-human
     chimeric IgG1/lambda antibody.  The chicken DD2 variable regions were
     humanized by transferring their CDRs and several framework amino acids
     onto human acceptor variable regions.  In the Vlambda, six chicken
     framework amino acids were identified to be important for the conformation
     of the CDR structure by computer modeling and therefore were retained in
     the humanized form; likewise, five chicken amino acids in the VH
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framework regions were retained in the humanized VH. The affinities of humanized DD2 IgG1/lambda to human and mouse IL-12 measured by competitive binding were nearly identical to those of chicken-human chimeric DD2 IgG1/lambda. This work demonstrates that humanization of chicken monoclonal antibodies assisted by computer modeling is possible, leading to a new way to generate therapeutic humanized antibodies against antigens to which the rodent immune system may fail to efficiently raise high affinity antibodies.

L32 ANSWER 2 OF 11 MEDLINE on STN

2003580200. PubMed ID: 14659749. A human synthetic combinatorial library of arrayable **single-chain** antibodies based on shuffling in vivo formed **CDRs** into general **framework regions**. Azriel-Rosenfeld Ronit; Valensi Moran; Benhar Itai. (Department of Molecular Microbiology and Biotechnology, The George S. Wise Faculty of Life Sciences, Green Building, Room 202, Tel-Aviv University, 69978, Ramat Aviv, Israel.) Journal of molecular biology, (2004 Jan 2) Vol. 335, No. 1, pp. 177-92. Journal code: 2985088R. ISSN: 0022-2836. Pub. country: England: United Kingdom. Language: English.

AB We describe a novel approach for high-throughput screening of recombinant antibodies, based on their immobilization on solid cellulose-based supports. We constructed a large human synthetic **single-chain** Fv antibody library where in vivo formed **complementarity determining regions** were shuffled combinatorially onto germline-derived human variable-region frameworks. The arraying of library-derived scFvs was facilitated by our unique display/expression system, where scFvs are expressed as fusion proteins with a cellulose-binding domain (CBD). Escherichia coli cells expressing library-derived scFv-CBDs are grown on a porous master filter on top of a second cellulose-based filter that captures the antibodies secreted by the bacteria. The cellulose filter is probed with labeled antigen allowing the identification of specific binders and the recovery of the original bacterial clones from the master filter. These filters may be simultaneously probed with a number of antigens allowing the isolation of a number of binding specificities and the validation of specificity of binders. We screened the library against a number of cancer-related peptides, proteins, and peptide-protein complexes and yielded antibody fragments exhibiting dissociation constants in the low nanomolar range. We expect our new antibody phage library to become a valuable source of antibodies to many different targets, and to play a vital role in facilitating high-throughput target discovery and validation in the area of functional cancer genomics.

L32 ANSWER 3 OF 11 MEDLINE on STN

2003519954. PubMed ID: 14597165. Characterization and molecular modeling of a highly stable anti-Hepatitis B surface antigen scFv. Bose Biplab; Chugh Dipti A; Kala Mrinalini; Acharya Subrat K; Khanna Navin; Sinha Subrata. (Department of Biochemistry, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, PIN-110029, India.) Molecular immunology, (2003 Dec) Vol. 40, No. 9, pp. 617-31. Journal code: 7905289. ISSN: 0161-5890. Pub. country: England: United Kingdom. Language: English.

AB We raised a mouse monoclonal antibody (5S) against the 'a' epitope of the Hepatitis B surface antigen (HBsAg) by selecting for binding of the hybridoma supernatant in conditions that usually destabilize protein-protein interactions. This antibody, which was protective in an in vitro assay, had a high affinity with a relative dissociation constant in the nanomolar range. It also displayed stable binding to antigen in conditions that usually destabilize antigen-antibody interactions, like 30% DMSO, 8 M urea, 4 M NaCl, 1 M guanidium HCl and extremes of pH. The variable regions of the antibody were cloned and expressed as an **single chain** variable fragment (scFv) (A5). A5 had a relative affinity comparable to the mouse monoclonal and showed antigen binding in presence of 20% DMSO, 8 M urea and 3 M NaCl. It bound the antigen in the pH range

of 6-8, though its tolerance for guanidium HCl was reduced. Sequence analysis demonstrated a significant increase in the frequency of somatic replacement mutations in **CDRs** over **framework regions** in the light but not in the heavy chain. A comparison of the molecular models of the variable regions of the 5S antibody and its germ-line precursor revealed that critical mutations in the heavy and light chains interface resulted in better inter-chain packing and in the movement of **CDR** H3 and **CDR** L1 from their germline positions, which may be important for better antigen binding. In addition to providing a reagent for neutralizing for the virus, such an antibody provides a model for the evolution of stable high affinity interaction during antibody maturation.

L32 ANSWER 4 OF 11 MEDLINE on STN

2002724653. PubMed ID: 12487314. Evolutionary affinity and selectivity optimization of a pesticide-selective antibody utlizing a hapten-selective immunoglobulin repertoire. Kramer Karl. (Technische Universitat Munchen, Center of Life Sciences Weihenstephan, Alte Akademie 12, D-85350 Freising, Germany.. kramer@wzw.tum.de) . Environmental science technology, (2002 Nov 15) Vol. 36, No. 22, pp. 4892-8. Journal code: 0213155. ISSN: 0013-936X. Pub. country: United States. Language: English.

AB Selectivity and sensitivity are considered as pivotal criteria for the quality of immunochemical assay designs in environmental analysis. They are essentially determined by the variable domains of the implemented antibody. The variable domains of a triazine-selective **single-chain** Fv (scFv) were genetically engineered by stringent molecular evolution in order to optimize analytical characteristics of the corresponding atrazine immunoassay. Gene variation of the template antibody by sequential shuffling against the variable heavy and light chain repertoire of a triazine-selective immunoglobulin library was enhanced by introducing additional point mutatons. Improved scFv variants were selected by phage display employing an atrazine derivative. By this means the paramounting affinity of the initial scFv to sebuthylazine was shifted for the mutant antibodies toward a preferential recognition of the envisaged target analyte atrazine. In addition, the detection limit of the atrazine assaywas significantly improved by factor 25 from 5.1 microg/L for the initial template antibody to 0.2 microg/L for the mutant antibodies. The contribution of the engineered antibody variants to the assay improvement is also reflected by a shift of the equilibrium dissociation constant KD from 1.27 x 10(-8) M of the template antibody to 7.46 x 10(-10) M of the optimized variant. Sequence analysis revealed a bias of amino acid substitutions in the first two **complementarity-determining regions** (**CDR**) and the flanking **framework regions** of both variable chains for the shuffled clones as well as a deletion in the **CDR3** of the light chain. Particularly the mutations of the VL domain turned out to have a decisive impact on the alterations in the analytical performance of the engineered scFv mutants. The application of the mutant antibodies for the atrazine determination of soil samples revealed consistency with HPLC data within the experimental error.

L32 ANSWER 5 OF 11 MEDLINE on STN

2002384444. PubMed ID: 12132587. Enzymatic characterization of glycosidase antibodies raised against a chair transition state analog and the retained catalytic activity from the expressed **single chain** antibody fragments. Choi So-Oung; Youn Hyun Joo; Yu Jaehoon. Molecules and cells, (2002 Jun 30) Vol. 13, No. 3, pp. 463-9. Journal code: 9610936. ISSN: 1016-8478. Pub. country: Korea (South). Language: English.

AB Catalytic antibodies with a glycosidase activity have been generated against a chair-like transition state analogue. Two monoclonal antibodies with the highest activity were selected for cloning and sequencing. Sequence analysis of the two antibodies showed four amino acids differences in the **framework region**. Such a difference resulted in 8-fold difference in catalytic activity with p-nitrophenyl-beta-D-

glucopyranoside between the two antibodies. Several Asp and Glu residues were found in the complimentarity determining region and some of these residue(s) might form the catalytic core for the glycosidase. Cloned antibody genes were expressed as a **single chain** antibody fragment. The expressed proteins showed the retained glycosidase activities.

L32 ANSWER 6 OF 11 MEDLINE on STN

2001144876. PubMed ID: 11132491. Construction, expression and activity test of a reshaping **single-chain** antibody against human CD3. Jiang X; Yu X C; Liu X F; Zhang W G; Huang H M; Lin Q; Sun J; Chen R S; Huang H L. (Institute of Genetics, Chinese Academy of Sciences, Beijing 100101, China.) Yi chuan xue bao = Acta genetica Sinica, (2000) Vol. 27, No. 9, pp. 762-71. Journal code: 7900784. ISSN: 0379-4172. Pub. country: China. Language: Chinese.

AB Monoclonal antibody (McAb) against human CD3 can adjust human body's immune statement in various ways, so that its clinical potential is highly regarded. In order to overcome the immunogenecity related to the murine McAb, this research effort was focused on constructing a reshaping **single-chain** antibody(scFv) against human CD3 employing antibody engineering. First, the **CDRs** of the murine McAb against human CD3 OKT3 was transplanted into the light-chain **framework regions** (FRs) of human McAb LS1 and the heavy-chain FRs of human McAb Nd respectively, spatial conformation was predicted by computer analysis. Then some particular residues were replaced in FRs basing on the result of conformational prediction to draw out the amino acid sequences of the reshaped VL and VH. The genes were chemically synthesize and inserted into an expression vector pROH80 to construct the reshaping scFv. Inducing the expression of reshaping scFv, the products are mainly as inclusion bodies. The reshaping scFv was expressed in another vector pALM. The inclusion bodies were denatured and then renatured by gel filtration. The renatured products were purified by immobilized metal affinity chromatograph (IMAC). Finally, the antigen-binding activily of the reshaping scFv against human CD3 was testified by the Compelitire in hibilory fluorescenceactivated cell sorting (FACS). The competitive inhibition rate is 18%.

L32 ANSWER 7 OF 11 MEDLINE on STN

1999321294. PubMed ID: 10395371. Inhibition of human immunodeficiency virus type 1 replication in vitro in acutely and persistently infected human CD4+ mononuclear cells expressing murine and humanized anti-human immunodeficiency virus type 1 Tat **single-chain** variable fragment intrabodies. Mhashilkar A M; LaVecchio J; Eberhardt B; Porter-Brooks J; Boisot S; Dove J H; Pumphrey C; Li X; Weissmahr R N; Ring D B; Ramstedt U; Marasco W A. (Department of Pathology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA.) Human gene therapy, (1999 Jun 10) Vol. 10, No. 9, pp. 1453-67. Journal code: 9008950. ISSN: 1043-0342. Pub. country: United States. Language: English.

AB We have previously reported that a murine anti-Tat **sFv** intrabody, termed sFvtat1Ck, directed against the proline-rich N-terminal activation domain of HIV-1, is a potent inhibitor of HIV-1 replication [Mhashilkar, A. M., et al. (1995). EMBO J. 14, 1542-1551]. In this study, the protective effect of sFvtat1Ck expression on HIV-1 replication in both acutely infected and persistently infected CD4+ cells was examined. Stably transfected CD4+ SupT1 cells were resistant to HIV-1 infection at high MOI with both the laboratory isolate HxB2 and six syncytium-inducing (SI) primary isolates. Persistently infected U1 cells, which can be induced to increase HIV-1 mRNA synthesis on addition of PMA or TNF-alpha, showed decreased production of HIV-1 in the presence of sFvtat1Ck. In transduced CD4+-selected, CD8+-depleted, and total PMBCs, the sFvtat1Ck-expressing cells showed marked inhibition of HIV-1 replication. The anti-Tat **sFv** was subsequently humanized by substituting compatible human **framework regions** that were chosen from a large database of human V(H) and V(L) sequences on the basis of high overall framework matching, similar **CDR**

length, and minimal mismatching of canonical and V(H)/V(L) contact residues. One humanized anti-Tat **sFv** intrabody, termed sFvhutat2, demonstrated a level of anti-HIV-1 activity that was comparable to the parental murine **sFv** when transduced PBMCs expressing the murine or humanized **sFv** intrabodies were challenged with HxB2 and two SI primary isolates. Because Tat is likely to have both direct and indirect effects in the pathogenesis of AIDS through its multiple roles in the HIV-1 life cycle and through its effects on the immune system, the strategy of genetically blocking Tat protein function with a humanized anti-Tat **sFv** intrabody may prove useful for the treatment of HIV-1 infection and AIDS, particularly when used as an adjuvant gene therapy together with highly active antiretroviral therapies that are currently available.

L32 ANSWER 8 OF 11 MEDLINE on STN

1999246121. PubMed ID: 10231090. Vernier zone residue 4 of mouse subgroup II kappa light chains is a critical determinant for antigen recognition. de Haard H; Kazemier B; van der Bent A; Oudshoorn P; Boender P; Arends J W; van Gemen B. (Biosciences Research Unit, Organon Teknika, Boxtel, The Netherlands.. hans-de.haard@unilever.com) . Immunotechnology : an international journal of immunological engineering, (1999 Mar) Vol. 4, No. 3-4, pp. 203-15. Journal code: 9511979. ISSN: 1380-2933. Pub. country: Netherlands. Language: English.

AB BACKGROUND: During the conversion of murine monoclonal antibodies directed against the human chorionic gonadotropin (hCG) into bacterially expressed **single chain** fragments (scFv), we found a major reduction of binding activity upon introduction of a primer encoded mutation. OBJECTIVES: In this study we tried to determine which mutation was responsible and on what manner this mutation affected antigen binding (structural effect versus direct involvement of the residue in binding). RESULTS: No binding could be detected, when the wild type residue methionine at position 4 within the **Framework region** 1 of the Vkappa light chain was substituted by serine in two antibodies with a subgroup II kappa light chain. However, a similar replacement within an anti-hCG antibody with a subgroup IV kappa light chain and thereby having leucine as wild type residue, did not affect the binding characteristics. The mutant scFv's derived from both AB-s sensitive for substitution by serine never reacted with antigen in ELISA. Analysis with surface plasmon resonance revealed a residual binding only on a sensorchip with a high density coating of antigen; however, an increased dissociation, relative to that of the wild type scFv and the absence of reactivity in ELISA suggest a drastically altered affinity. CONCLUSION: A structural explanation for the changed binding characteristics can be the influence of the position 4 residue, as being a constituent of the Vernier zone, on the position of the **CDR1** loop of Vkappa, which might harbour residues that directly bind to antigen, or indirectly positions other variable loops of the binding pocket. An increased sensitivity for trypsin digestion supported the hypothesis of a local conformational change in the serine mutant of the subgroup II kappa containing antibody.

L32 ANSWER 9 OF 11 MEDLINE on STN

97315893. PubMed ID: 9171898. Inhibition of complement activity by humanized anti-C5 antibody and **single-chain** Fv. Thomas T C; Rollins S A; Rother R P; Giannoni M A; Hartman S L; Elliott E A; Nye S H; Matis L A; Squinto S P; Evans M J. (Alexion Pharmaceuticals, New Haven, CT 06511, USA.) Molecular immunology, (1996 Dec) Vol. 33, No. 17-18, pp. 1389-401. Journal code: 7905289. ISSN: 0161-5890. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Activation of the complement system contributes significantly to the pathogenesis of numerous acute and chronic diseases. Recently, a monoclonal antibody (5G1.1) that recognizes the human complement protein C5, has been shown to effectively block C5 cleavage, thereby preventing the generation of the pro-inflammatory complement components C5a and

C5b-9. Humanized 5G1.1 antibody, Fab and scFv molecules have been produced by grafting the **complementarity determining regions** of 5G1.1 on to human **framework regions**. Competitive ELISA analysis indicated that no framework changes were required in the humanized variable regions for retention of high affinity binding to C5, even at framework positions predicted by computer modeling to influence CDR canonical structure. The humanized Fab and scFv molecules blocked complement-mediated lysis of chicken erythrocytes and porcine aortic endothelial cells in a dose-dependent fashion, with complete complement inhibition occurring at a three-fold molar excess, relative to the human C5 concentration. In contrast to a previously characterized anti-C5 scFv molecule, the humanized h5G1.1 scFv also effectively blocked C5a generation. Finally, an intact humanized h5G1.1 antibody blocked human complement lytic activity at concentrations identical to the original murine monoclonal antibody. These results demonstrate that humanized h5G1.1 and its recombinant derivatives retain both the affinity and blocking functions of the murine 5G1.1 antibody, and suggest that these molecules may serve as potent inhibitors of complement-mediated pathology in human inflammatory diseases.

L32 ANSWER 10 OF 11 MEDLINE on STN

95062162. PubMed ID: 7971973. Autoantibodies to the alpha/beta T-cell receptors in human immunodeficiency virus infection: dysregulation and mimicry. Lake D F; Schluter S F; Wang E; Bernstein R M; Edmundson A B; Marchalonis J J. (College of Medicine, University of Arizona, Tucson 85724.) Proceedings of the National Academy of Sciences of the United States of America, (1994 Nov 8) Vol. 91, No. 23, pp. 10849-53. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Autoimmune reactivity is a consequence of infection with human immunodeficiency virus (HIV). We studied serological cross-reactions of purified pooled IgG from sera of HIV-infected individuals by using nested sets of synthetic overlapping peptides duplicating the covalent structures of T-cell receptors (TCRs) and immunoglobulin light chains and report that two processes of autoantibody production occur. (i) IgG autoantibodies to putative regulatory variable domain **CDR1** and FR3 epitopes (where **CDR** is **complementarity-determining region** and FR is **framework region**) are present in pooled IgG from HIV-infected individuals at levels 10-fold greater than that in pooled IgG from healthy humans. (ii) Anti-TCR autoimmunization involves antigenic mimicry between a conserved peptide stretch of the major neutralizing V3 loop determinant of HIV-1 gp120 and the conserved FR4 segment of the TCR V beta. Affinity-purified antibodies to the synthetic V3 loop peptide bound to a recombinant **single-chain** TCR and to a synthetic TCR joining segment peptide containing the FR4 sequence. Conversely, affinity-purified autoantibodies from pooled IgG from HIV-infected individuals to the TCR peptide bound the V3 loop peptide and a **single-chain** TCR. Inhibition studies indicated that the cross-reactive immunizing antigen was the V3 loop. These results bear upon the impact of HIV infection on immune regulation and on the selection of peptides for vaccine development.

L32 ANSWER 11 OF 11 MEDLINE on STN

94352969. PubMed ID: 8073039. Engineering interchain disulfide bonds into conserved **framework regions** of Fv fragments: improved biochemical characteristics of recombinant immunotoxins containing disulfide-stabilized Fv. Reiter Y; Brinkmann U; Webber K O; Jung S H; Lee B; Pastan I. (Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.) Protein engineering, (1994 May) Vol. 7, No. 5, pp. 697-704. Journal code: 8801484. ISSN: 0269-2139. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Using molecular modeling technology, we have recently identified two positions in conserved **framework regions** of antibody Fv fragments

(Fvs) that are distant from **CDRs**, and potentially can be used to make recombinant Fv fragments in which the unstable VH and VL heterodimer is stabilized by an interchain disulfide bond inserted between structurally conserved framework positions. A disulfide bond has been introduced at one of these positions, VH44-VL105, and shown to stabilize various Fvs that retain full binding and specificity. Recombinant immunotoxins, e.g. B3(dsFv)-PE38KDEL in which this disulfide-stabilized Fv moiety is connected to a truncated form of Pseudomonas exotoxin (PE; PE38KDEL) which contains the translocation and ADP ribosylation domains, are indistinguishable in binding and specificity from its **single-chain** immunotoxin counterparts. We have now analyzed the alternative position, (VH111-VL48), predicted by the modeling methodology, for disulfide stabilization of mAb B3(Fv) by producing a recombinant immunotoxin with such disulfide-stabilized (ds) Fv. This immunotoxin was also very active and retained full specificity to B3 antigen-positive cells. However, it was 2- to 3-fold less active than the VH44-VL105 dsFv-molecule. We also tested various biochemical features of VH44-VL105 and VH111-VL48 dsFv immunotoxins and compared them with the corresponding **single-chain** immunotoxin. We found the dsFv immunotoxins were more stable in human serum and more resistant to thermal and chemical denaturation than the **single chain** (sc) Fv immunotoxin. Because dsFv immunotoxins and dsFvs have full activity and specificity and improved stability, they may be more useful than scFv immunotoxins as therapeutic and diagnostic agents.

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=> d his

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     FILE 'USPATFULL' ENTERED AT 20:15:17 ON 27 SEP 2006
                E HUSTON JAMES S/IN
L1           26 S E3
L2            7 S L1 AND (FRAMEWORK REGION?/CLM)
                E OPPERMANN H/AU
                E E12
L3          101 S E3-E5
L4           84 S L3 NOT L1
L5            0 S L4 AND (FRAMEWORK REGION?/CLM)

     FILE 'WPIDS' ENTERED AT 20:20:02 ON 27 SEP 2006
                E HUSTON J S/IN
L6           20 S E3
L7            9 S L6 AND (FRAMEWORK REGION?)
                E OPPERMANN H/IN
L8          138 S E3
L9          126 S L8 NOT L6
L10           0 S L9 AND (FRAMEWORK REGION?)

     FILE 'MEDLINE' ENTERED AT 20:23:24 ON 27 SEP 2006
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L11          35 S E3
L12           0 S L11 AND (FRAMEWORK REGION?)
                E OPPERMANN H/AU
L13          75 S E3
L14          65 S L13 NOT L11
L15           1 S L14 AND (FRAMEWORK)

     FILE 'USPATFULL' ENTERED AT 20:32:29 ON 27 SEP 2006
L16         380 S (FRAMEWORK REGION?/CLM)
L17         197 S L16 AND (COMPLEMENTARITY DETERMINING REGION?/CLM)
L18          17 S L17 AND LINKER/CLM
L19          11 S L18 NOT L1
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L20          16 S (BIOSYNTHETIC ANTIBODY BINDING SITE?/CLM OR BABS/CLM)
L21          15 S L20 NOT L1
L22          15 S L21 NOT L19
L23        1098 S (SINGLE-CHAIN FV/CLM OR SCFV/CLM OR SFV/CLM)
L24           2 S L23 AND (PREDETERMINED ANTIGEN/CLM)
L25           2 S L24 NOT L1

     FILE 'WPIDS' ENTERED AT 20:38:30 ON 27 SEP 2006
L26         365 S (FRAMEWORK REGION?)
L27         187 S L26 AND (COMPLEMENTARITY DETERMINING REGION?)
L28          14 S L27 AND LINKER
L29           7 S L28 NOT L6

     FILE 'MEDLINE' ENTERED AT 20:44:39 ON 27 SEP 2006
L30         415 S (FRAMEWORK REGION?)
L31         221 S L30 AND (COMPLEMENTARITY DETERMINING REGION? OR CDR?)
L32          11 S L31 AND (SINGLE-CHAIN OR SFV)

=> s (biosynthetic antibody binding sites)
         18084 BIOSYNTHETIC
        459248 ANTIBODY
        780615 BINDING
        450905 SITES
L33          1 (BIOSYNTHETIC ANTIBODY BINDING SITES)
                (BIOSYNTHETIC(W)ANTIBODY(W)BINDING(W)SITES)

=> d l33,cbib,ab

L33  ANSWER 1 OF 1     MEDLINE on STN
92272920.    PubMed ID: 1815591.   Biosynthetic antibody binding sites:
     development of a single-chain Fv model based on antidinitrophenol IgA
     myeloma MOPC 315. McCartney J E; Lederman L; Drier E A; Cabral-Denison N
     A; Wu G M; Batorsky R S; Huston J S; Oppermann H. (Creative BioMolecules,
     Inc., Hopkinton, Massachusetts 01748. ) Journal of protein chemistry,
     (1991 Dec) Vol. 10, No. 6, pp. 669-83.  Ref: 52. Journal code: 8217321.
     ISSN: 0277-8033. Pub. country: United States. Language: English.
AB   The functional antigen binding region of antidinitrophenol mouse IgA
     myeloma MOPC 315 has been produced as a single-chain Fv (sFv) protein in
     E. coli.  Recombinant 315 proteins included sFv alone, a bifunctional
     fusion protein with amino-terminal fragment B (FB) of staphylococcal
     protein A, and a two-chain 315 Fv fragment.  Successful refolding of the
     315 sFv required formation of disulfide bonds while the polypeptide was in
     a denatured state, as previously observed for the parent Fv fragment.
     Affinity-purified recombinant 315 proteins showed full recovery of
     specific activity, with values for Ka,app of 1.5 to 2.2 x 10(6) M-1,
     equivalent to the parent 315 Fv fragment.  As observed for natural 315 Fv,
     the sFv region of active FB-sFv315 fusion protein was resistant to pepsin
     treatment, whereas inactive protein was readily degraded.  These
     experiments will allow the application of protein engineering to the 315
     single-chain Fv; such studies can advance structure-function studies of
     antibody combining sites and lead to an improved understanding of
     single-chain Fv proteins.


=> d his

     (FILE 'HOME' ENTERED AT 20:15:09 ON 27 SEP 2006)

     FILE 'USPATFULL' ENTERED AT 20:15:17 ON 27 SEP 2006
               E HUSTON JAMES S/IN
L1           26 S E3
L2            7 S L1 AND (FRAMEWORK REGION?/CLM)
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                E OPPERMANN H/AU
                E E12
L3          101 S E3-E5
L4           84 S L3 NOT L1
L5            0 S L4 AND (FRAMEWORK REGION?/CLM)

     FILE 'WPIDS' ENTERED AT 20:20:02 ON 27 SEP 2006
                E HUSTON J S/IN
L6           20 S E3
L7            9 S L6 AND (FRAMEWORK REGION?)
                E OPPERMANN H/IN
L8          138 S E3
L9          126 S L8 NOT L6
L10           0 S L9 AND (FRAMEWORK REGION?)

     FILE 'MEDLINE' ENTERED AT 20:23:24 ON 27 SEP 2006
                E HUSTON J S/AU
L11          35 S E3
L12           0 S L11 AND (FRAMEWORK REGION?)
                E OPPERMANN H/AU
L13          75 S E3
L14          65 S L13 NOT L11
L15           1 S L14 AND (FRAMEWORK)

     FILE 'USPATFULL' ENTERED AT 20:32:29 ON 27 SEP 2006
L16         380 S (FRAMEWORK REGION?/CLM)
L17         197 S L16 AND (COMPLEMENTARITY DETERMINING REGION?/CLM)
L18          17 S L17 AND LINKER/CLM
L19          11 S L18 NOT L1
L20          16 S (BIOSYNTHETIC ANTIBODY BINDING SITE?/CLM OR BABS/CLM)
L21          15 S L20 NOT L1
L22          15 S L21 NOT L19
L23        1098 S (SINGLE-CHAIN FV/CLM OR SCFV/CLM OR SFV/CLM)
L24           2 S L23 AND (PREDETERMINED ANTIGEN/CLM)
L25           2 S L24 NOT L1

     FILE 'WPIDS' ENTERED AT 20:38:30 ON 27 SEP 2006
L26         365 S (FRAMEWORK REGION?)
L27         187 S L26 AND (COMPLEMENTARITY DETERMINING REGION?)
L28          14 S L27 AND LINKER
L29           7 S L28 NOT L6

     FILE 'MEDLINE' ENTERED AT 20:44:39 ON 27 SEP 2006
L30         415 S (FRAMEWORK REGION?)
L31         221 S L30 AND (COMPLEMENTARITY DETERMINING REGION? OR CDR?)
L32          11 S L31 AND (SINGLE-CHAIN OR SFV)
L33           1 S (BIOSYNTHETIC ANTIBODY BINDING SITES)

=> log off
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
STN INTERNATIONAL LOGOFF AT 20:48:24 ON 27 SEP 2006
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